

CYCLOPROPYL COMPOUNDS AS CCR5 ANTAGONISTS

BACKGROUND OF THE INVENTION

5 The human immunodeficiency virus ("HIV") is the causative agent for acquired immunodeficiency syndrome ("AIDS"), a disease characterized by the destruction of the immune system, particularly of CD4⁺ T-cells, with attendant susceptibility to opportunistic infections, and its precursor AIDS-related complex ("ARC"), a syndrome characterized by symptoms such as persistent generalized 10 lymphadenopathy, fever and weight loss.

In addition to CD4, HIV requires a co-receptor for entry into target cells. The chemokine receptors function together with CD4 as co-receptors for HIV. The chemokine receptors CXCR4 and CCR5 have been identified as the main co-receptors for HIV-1. CCR5 acts as a major co-receptor for fusion and entry of 15 macrophage-tropic HIV into host cells. These chemokine receptors are thought to play an essential role in the establishment and dissemination of an HIV infection. Therefore, CCR5 antagonists are thought to be useful as therapeutic agents active 20 against HIV.

We have now discovered a series of small molecule nonpeptide compounds that are useful as inhibitors of HIV replication.

BRIEF DESCRIPTION OF THE INVENTION

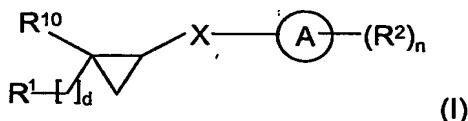
25 The present invention features compounds that are useful in the inhibition of HIV replication, the prevention of infection by HIV, the treatment of infection by HIV and in the treatment of AIDS and/or ARC, either as pharmaceutically acceptable salts or pharmaceutical composition ingredients. The present invention further features 30 methods of treating AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV as monotherapy or in combination with other antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. The present invention also features pharmaceutical compositions, comprising the above-mentioned compounds that are suitable for the prevention or treatment of CCR5-related diseases and

conditions. The present invention further features processes for making the above-mentioned compounds.

SUMMARY OF THE PRESENT INVENTION

The present invention includes compounds of formula (I):

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or pharmaceutically acceptable derivatives thereof, wherein:

X is a C₁₋₅ alkylene chain, wherein said X is optionally substituted by one or more =O, =S, alkyl, or halogen and wherein said C₁₋₅ alkylene chain may optionally have 0-3 heteroatoms selected from oxygen, phosphorus, sulfur, or nitrogen;

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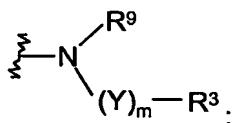
Ring A is a saturated, partially saturated or aromatic 3-7 monocyclic or 8-10 membered bicyclic ring having one ring nitrogen and 0-4 additional heteroatoms selected from oxygen, phosphorus, sulfur, or nitrogen;

R¹ is selected from the group consisting of

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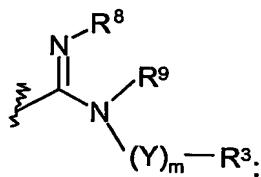
(a) a saturated, partially saturated, or aromatic 4-7 monocyclic or 8-10 membered bicyclic ring having one ring nitrogen and 0-4 additional heteroatoms selected from oxygen, phosphorus, sulfur, or nitrogen, optionally attached through a C₁₋₆ alkylene chain, and optionally substituted by one or more R⁸;

(b)

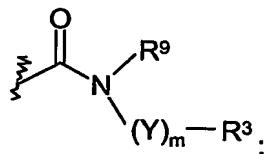


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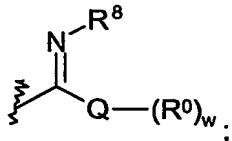
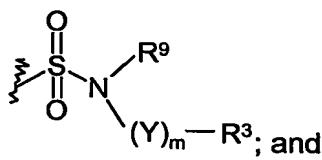
(c)



(d)



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Q is carbon, oxygen, or S(O);

w is 1 or 2;

5 each R² is independently selected from the group consisting of -OR⁰,
 $-\text{C}(\text{O})\text{R}^0$, $-\text{S}(\text{O})_2\text{R}^0$, $-\text{C}(\text{O})\text{N}(\text{R}^0)_2$, $-\text{S}(\text{O})_2\text{N}(\text{R}^0)_2$, $-(\text{CH}_2)_a\text{N}(\text{R}^0)(-\text{V}_b\text{R}^+)$,
 $-(\text{CH}_2)_a(-\text{V}_b\text{R}^+)$, halogen, alkyl optionally substituted by one or more R⁷, alkenyl
optionally substituted by one or more R⁷, alkynyl optionally substituted by one or
more R⁷, aryl optionally substituted by one or more R⁸, heteroaryl optionally
10 substituted by one or more R⁸, cycloalkyl optionally substituted by one or more R⁸,
and heterocyclyl optionally substituted by one or more R⁸; and two adjacent R²s on
Ring A are optionally taken together to form a fused, saturated, partially saturated or
aromatic 5-6 membered ring having 0-3 heteroatoms selected from oxygen,
phosphorus, sulfur, or nitrogen; or two geminal R²s are optionally taken together to
15 form a spiro, saturated, partially saturated or aromatic 5-6 membered ring having 0-3
heteroatoms selected from oxygen, phosphorus, sulfur, or nitrogen, said fused or
spiro ring being optionally substituted by one or more R⁸;

each a independently is 0-3;

each b independently is 0 or 1;

20 V is $-\text{C}(\text{O})$, $-\text{C}(\text{O})\text{O}$, $-\text{S}(\text{O})_2$, or $-\text{C}(\text{O})\text{N}(\text{R}^0)$;

R⁺ is alkyl, cycloalkyl, aralkyl, aryl, heteroaryl, heteroaralkyl, or heterocyclyl,
wherein said R⁺ is optionally substituted by one or more R⁸;

25 d is 0-3;

m is 0 or 1;

n is 0-5;

30 R³ is H, $-\text{N}(\text{R}^0)_2$, $-\text{N}(\text{R}^0)\text{C}(\text{O})\text{R}^0$, $-\text{CN}$, halogen, CF_3 , alkyl optionally substituted
by one or more groups selected from R⁷ or -S-aryl optionally substituted by
 $-(\text{CH}_2)_{1-6}\text{N}(\text{R}^0)\text{SO}_2(\text{R}^0)$, alkenyl optionally substituted by one or more groups selected
from R⁷ or -S-aryl optionally substituted by $-(\text{CH}_2)_{1-6}\text{N}(\text{R}^0)\text{SO}_2(\text{R}^0)$, alkynyl optionally
substituted by one or more groups selected from R⁷ or -S-aryl optionally substituted
by $-(\text{CH}_2)_{1-6}\text{N}(\text{R})\text{SO}_2(\text{R}^0)$, cycloalkyl or carbocyclyl optionally substituted by one or

more R⁸, aryl optionally substituted by one or more R⁶, heteroaryl optionally substituted by one or more R⁶, or heterocycll optionally substituted by one or more R⁸;

Y is alkyl, alkenyl, alkynyl, -(CR⁴R⁵)_p-, -C(O)-, -C(O)C(O)-, -C(S)-,

5 -O-(CH₂)₀₋₄-C(O)-, -(CH₂)₀₋₄-C(O)-O-, -N(R⁰)-C(O)-, -C(O)-N(R⁰)-, -N(R⁰)-C(S)-, -S(O)_t-, -O-C(=N-CN)-, -O-C(=N-R⁰)-, -C(=N-CN)-O-, -C(=N-CN)-S-, -C(=N-R⁰)-O-, -S-C(=N-CN)-, -N(R⁰)-C(=N-CN)-, -C(=N-CN)-, -N(R⁰)-C[=N-C(O)-R⁰], -N(R⁰)-C[=N-S(O)_t-R⁰], -N(R⁰)-C(=N-OR⁰)-, -N(R⁰)-C(=N-R⁰)-, or -C(=N-R⁰)-;

each R⁴ is independently H or alkyl optionally substituted by R⁷, alkenyl

10 optionally substituted by R⁷, or alkynyl optionally substituted by R⁷;

each R⁵ is independently selected from the group consisting of H, -C(O)-OR⁸, -C(O)-N(R⁰)₂, -S(O)_t-N(R⁰)₂, -S(O)_t-R⁰, aryl optionally substituted by R⁶, and heteroaryl optionally substituted by R⁶;

p is 1-5;

15 each t independently is 1 or 2;

each R⁸ is independently selected from the group consisting of halogen, -CF₃, -OCF₃, -OR⁰, -(CH₂)₁₋₆-OR⁰, -SR⁰, -(CH₂)₁₋₆-SR⁰, -SCF₃, -R⁰, methylenedioxy, ethylenedioxy, -NO₂, -CN, -(CH₂)₁₋₆-CN, -N(R⁰)₂, -(CH₂)₁₋₆-N(R⁰)₂, -NR⁰C(O)R⁰, -NR⁰(CN), -NR⁰C(O)N(R⁰)₂, -NR⁰C(S)N(R⁰)₂, -NR⁰CO₂R⁰, -NR⁰NR⁰C(O)R⁰,

20 -NR⁰NR⁰C(O)N(R⁰)₂, -NR⁰NR⁰CO₂R⁰, -C(O)C(O)R⁰, -C(O)CH₂C(O)R⁰, -(CH₂)₀₋₆CO₂R⁰, -O-C(O)R⁰, -C(O)R⁰, -C(O)N(R⁰)N(R⁰)₂, -C(O)N(R⁰)₂, -C(O)N(R⁰)OH, -C(O)N(R⁰)SO₂R⁰, -OC(O)N(R⁰)₂, -S(O)_tR⁰, -S(O)_t-OR⁰, -S(O)_tN(R⁰)C(O)R⁰, -S(O)_tN(R⁰)OR⁰, -NR⁰SO₂N(R⁰)₂, -NR⁰SO₂R⁰, -C(=S)N(R⁰)₂, -C(=NH)-N(R⁰)₂, -(CH₂)₁₋₆-C(O)R⁰, -C(=N-OR⁰)-N(R⁰)₂, -O-(CH₂)₀₋₆-SO₂N(R⁰)₂, -(CH₂)₁₋₆NHC(O)R⁰,

25 and -SO₂N(R⁰)₂ wherein the two R⁰'s on the same nitrogen are optionally taken together to form a 5-8 membered saturated, partially saturated, or aromatic ring having additional 0-4 heteroatoms selected from oxygen, phosphorus, nitrogen, or sulfur;

each R⁷ is independently selected from the group consisting of halogen, -CF₃,

30 -R⁰, -OR⁰, -OCF₃, -(CH₂)₁₋₆-OR⁰, -SR⁰, -SCF₃, -(CH₂)₁₋₆-SR⁰, aryl optionally substituted by R⁶, methylenedioxy, ethylenedioxy, -NO₂, -CN, -(CH₂)₁₋₆-CN, -N(R⁰)₂, -(CH₂)₁₋₆-N(R⁰)₂, -NR⁰C(O)R⁰, -NR⁰(CN), -NR⁰C(O)N(R⁰)₂, -N(R⁰)C(S)N(R⁰)₂, -NR⁰CO₂R⁰, -NR⁰NR⁰C(O)R⁰, -NR⁰NR⁰C(O)N(R⁰)₂, -NR⁰NR⁰CO₂R⁰, -C(O)C(O)R⁰, -C(O)CH₂C(O)R⁰, -(CH₂)₀₋₆-CO₂R⁰, -C(O)R⁰, -C(O)N(R⁰)N(R⁰)₂, -C(O)N(R⁰)₂,

-C(O)N(R⁰)OH, -OC(O)R⁰, -C(O)N(R⁰)SO₂R⁰, -OC(O)N(R⁰)₂, -S(O)_tR⁰, -S(O)_tOR⁰, -S(O)_tN(R⁰)C(O)R⁰, -S(O)_tN(R⁰)OR⁰, -NR⁰SO₂N(R⁰)₂, -NR⁰SO₂R⁰, -C(=S)N(R⁰)₂, -C(=NH)-N(R⁰)₂, -(CH₂)₁₋₆-C(O)R⁰, -C(=N-OR⁰)-N(R⁰)₂, -O-(CH₂)₀₋₆-SO₂N(R⁰)₂, -(CH₂)₁₋₆-NHC(O)R⁰, and -SO₂N(R⁰)₂ wherein the two R⁰'s on the same nitrogen are

5 optionally taken together to form a 5-8 membered saturated, partially saturated, or aromatic ring having additional 0-4 heteroatoms selected from oxygen, phosphorus, nitrogen, or sulfur;

each R⁸ independently is selected from the group consisting of R⁷, =O, =S, =N(R⁰), and =N(CN);

10 R⁹ is hydrogen, alkyl optionally substituted by one or more R⁷, alkenyl optionally substituted by one or more R⁷, alkynyl optionally substituted by one or more R⁷, cycloalkyl optionally substituted by one or more R⁸, heterocyclyl optionally substituted by one or more R⁸, heteroaryl optionally substituted by one or more R⁸, or aryl optionally substituted by one or more R⁶; or

15 -(Y)_m-R³ and R⁹ may combine with the nitrogen atom with which they are attached to form a saturated, partially saturated, or aromatic 5-7 membered monocyclic or 8-10 membered bicyclic ring that optionally contains 1 to 3 additional heteroatoms selected oxygen, phosphorus, sulfur, or nitrogen, wherein said ring may be optionally substituted with one or more R⁸;

20 R¹⁰ is hydrogen, alkyl optionally substituted by one or more R⁷, alkenyl optionally substituted by one or more R⁷, alkynyl optionally substituted by one or more R⁷, cycloalkyl optionally substituted by one or more R⁸, heterocyclyl optionally substituted by one or more R⁸, heteroaryl optionally substituted by one or more R⁶, or aryl optionally substituted by one or more R⁶;

25 each R⁰ is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, carbocyclylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl, and heterocyclylalkyl, wherein each member of R⁰ except H is optionally substituted by one or more R*, OR*, N(R*)₂, =O, =S, halogen, CF₃, NO₂, CN, -C(O)R*, -CO₂R*, -C(O)-aryl, -C(O)-heteroaryl, -C(O)aralkyl, -S(O)_t-aryl, -S(O)_t-heteroaryl, -NR^{*}SO₂R*, -NR^{*}C(O)R*, -NR^{*}C(O)N(R*)₂, -N(R*)C(S)N(R*)₂, -NR^{*}CO₂R*, -NR^{*}NR^{*}C(O)R*, -NR^{*}NR^{*}C(O)N(R*)₂, -NR^{*}NR^{*}CO₂R*, -C(O)C(O)R*, -C(O)CH₂C(O)R*, -C(O)N(R*)N(R*)₂, -C(O)N(R*)₂, -C(O)NR^{*}SO₂R*, -OC(O)N(R*)₂, -S(O)_tR*, -NR^{*}SO₂N(R*)₂, -SO₂N(R*)₂ wherein the two R*'s on the same nitrogen are optionally taken together to form a 5-8 membered saturated, partially saturated, or

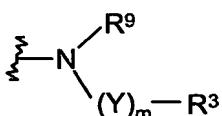
aromatic ring having additional 0-4 heteroatoms selected from oxygen, phosphorus, nitrogen, or sulfur; and

each R* is independently H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, or heteroaryl.

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In one embodiment, suitably R¹⁰ is optionally substituted aryl, such as optionally substituted phenyl.

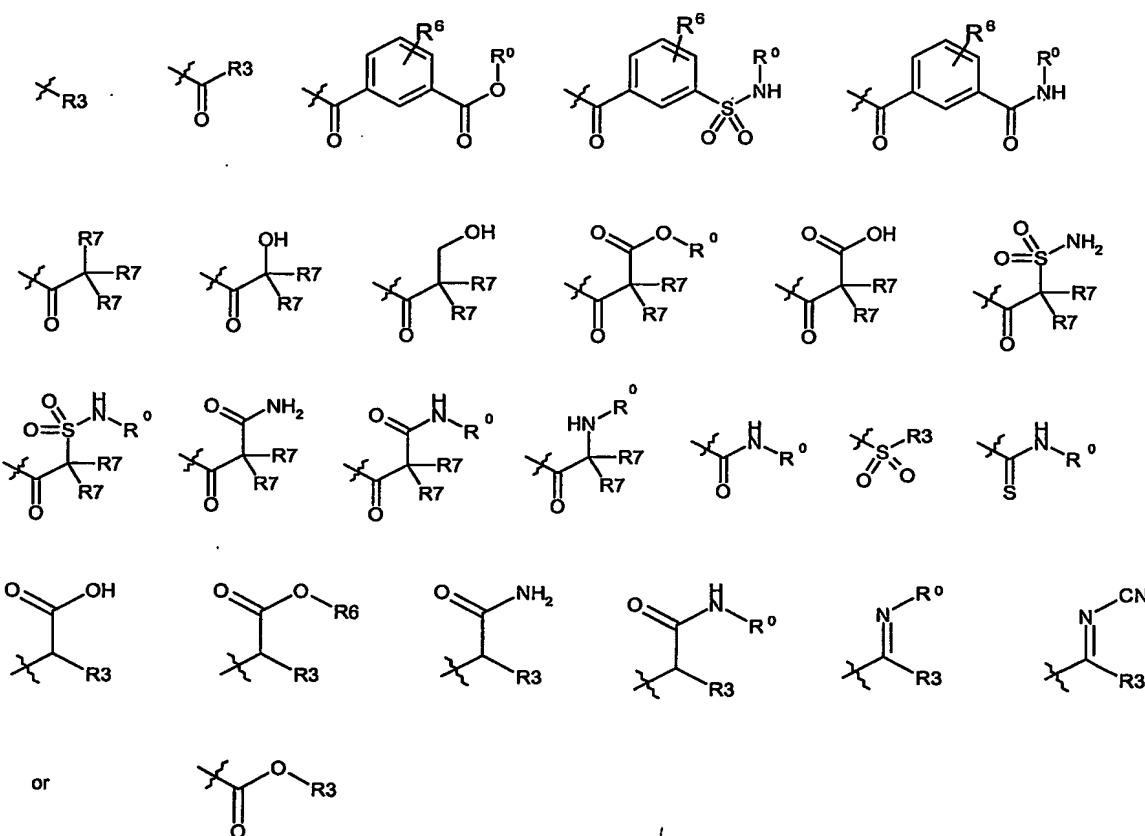
In one embodiment, R¹ is



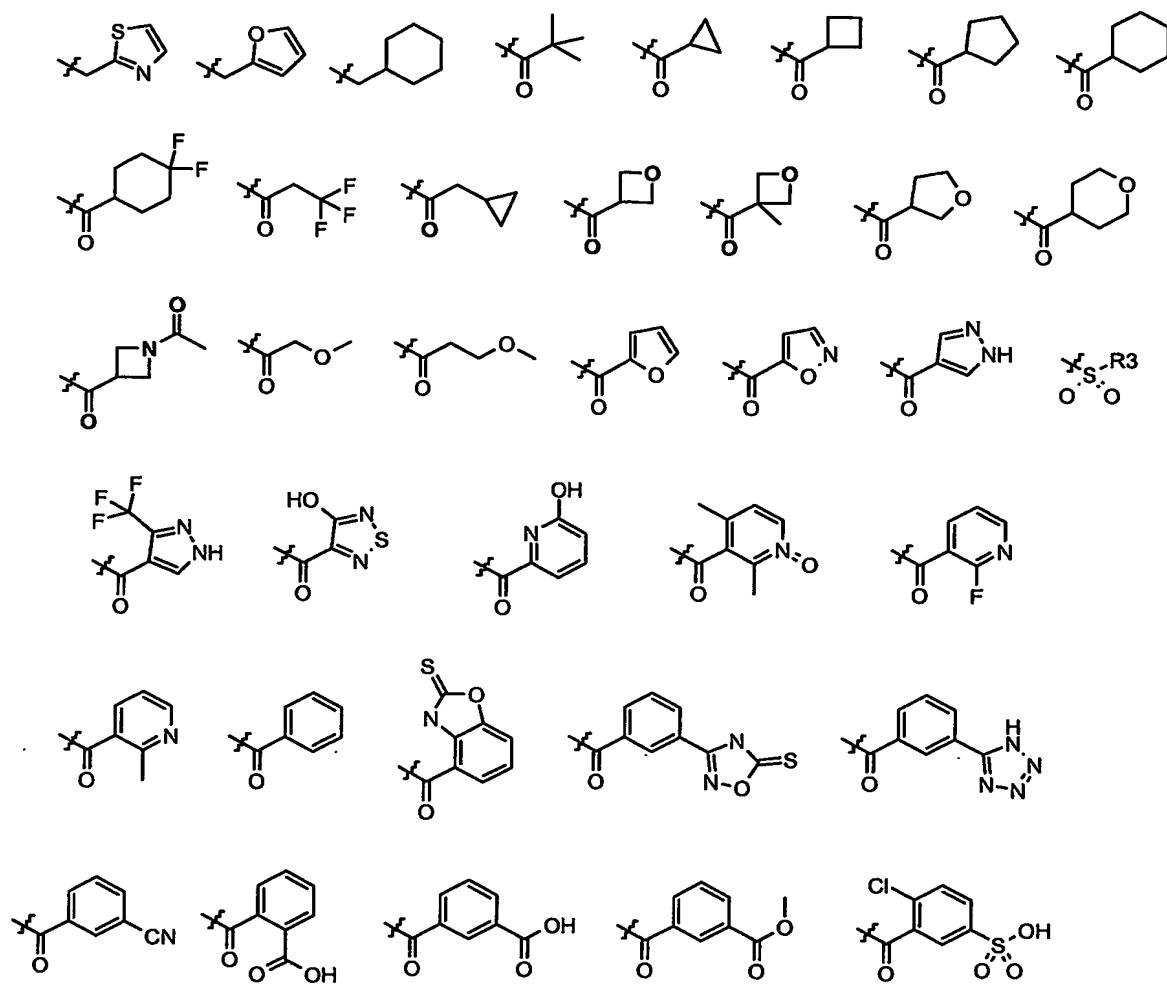
In one embodiment R⁹ is alkyl and preferably R⁹ is methyl.

In one embodiment $-(\text{Y})_m\text{---R}^3$ suitably is

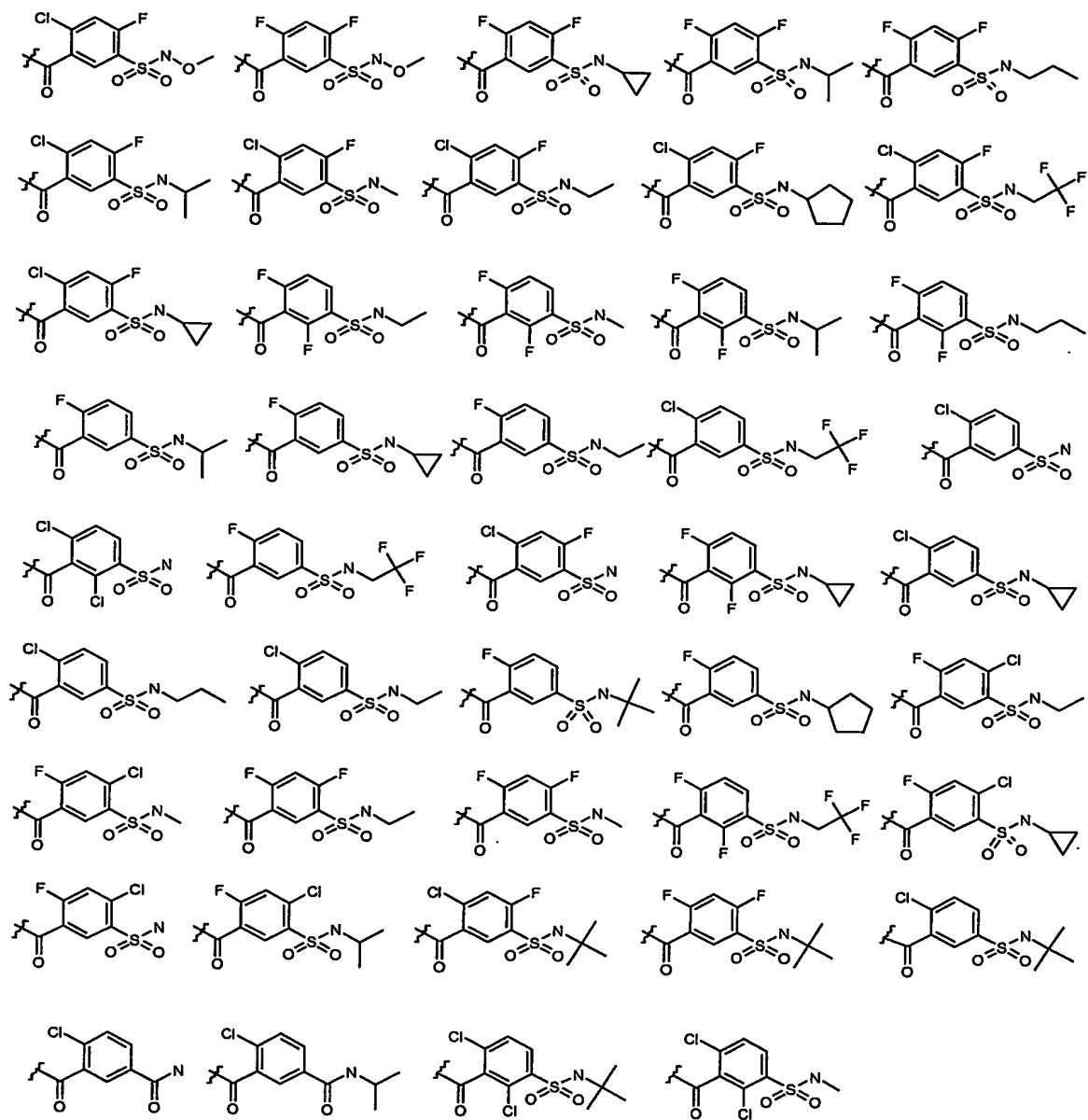
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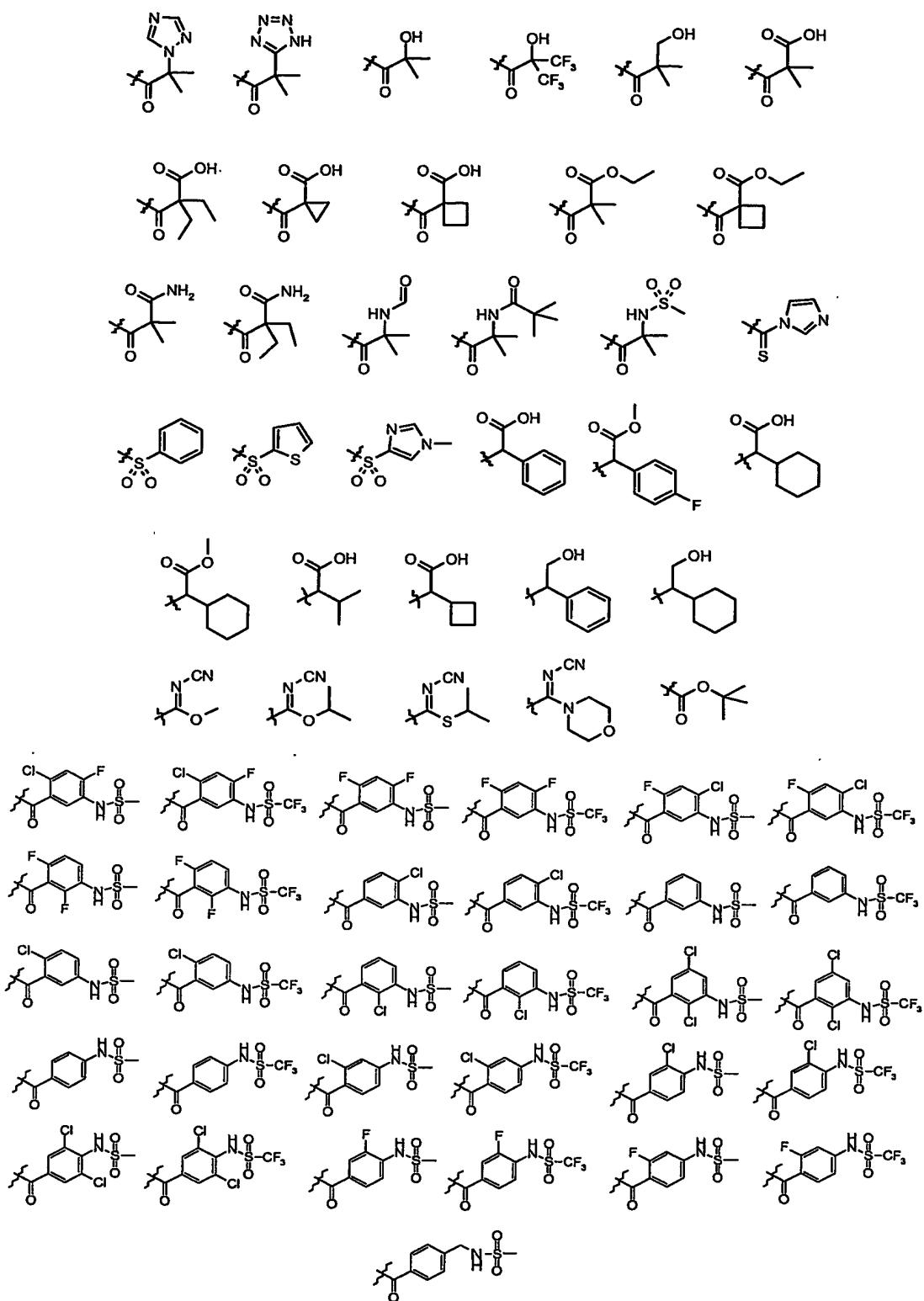


More suitably $-(Y)_m-R^3$ is

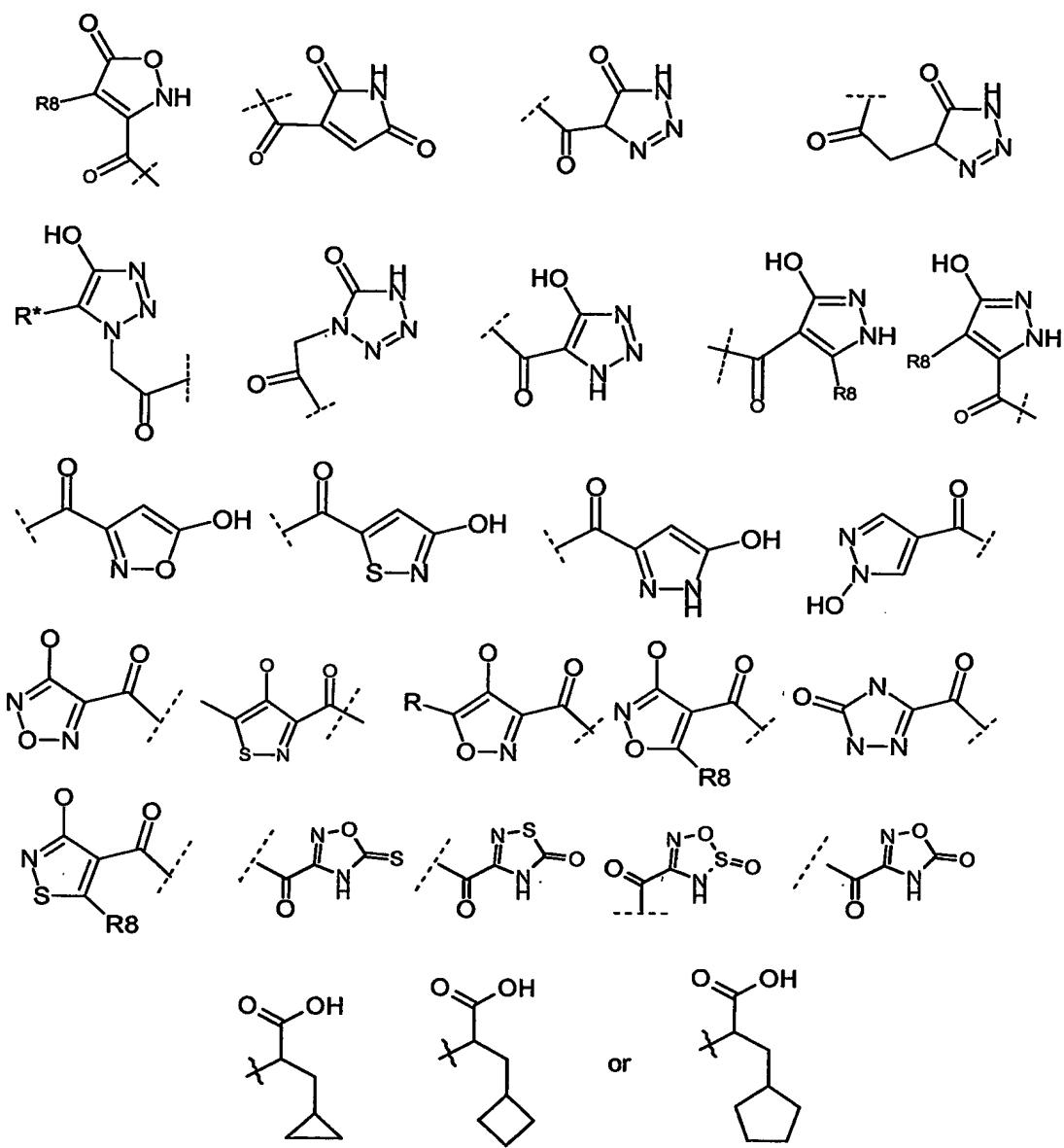


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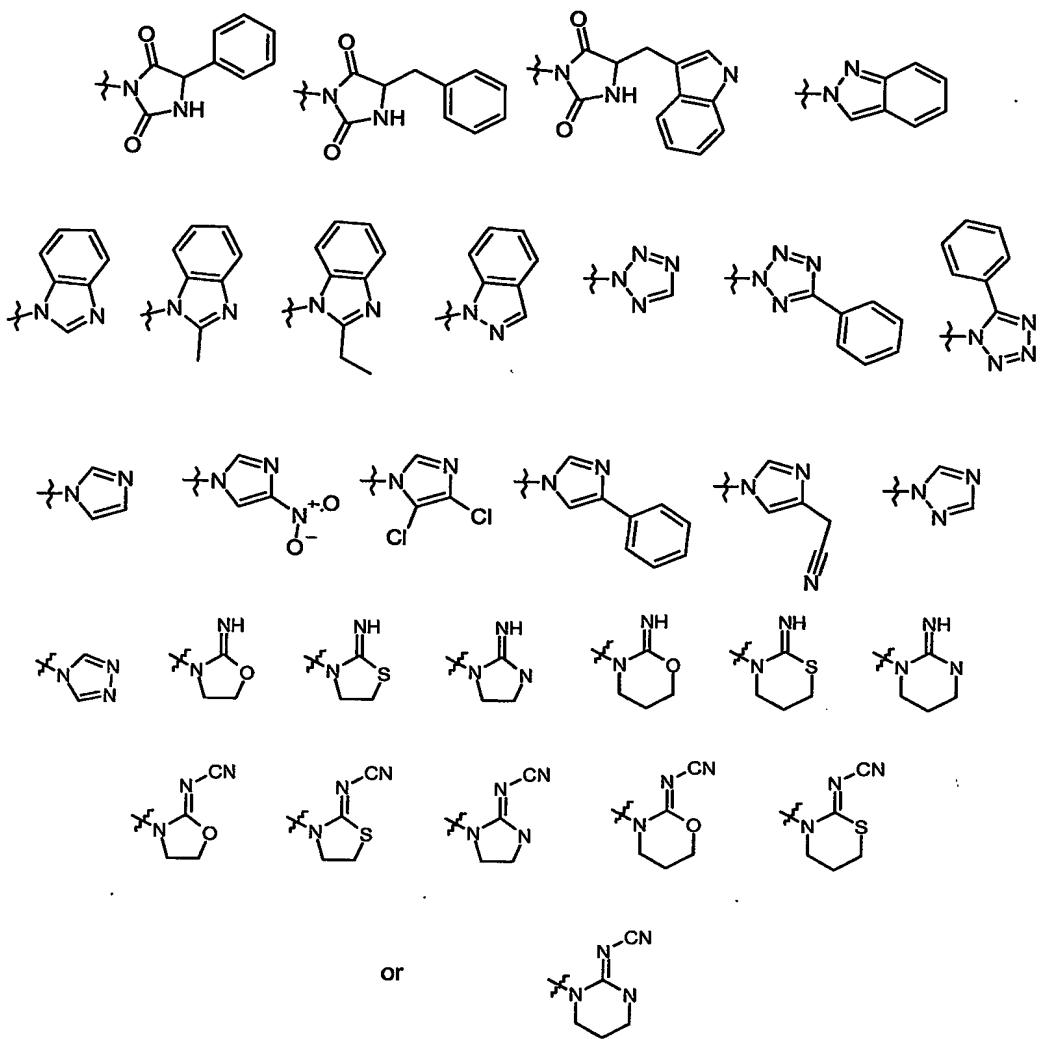


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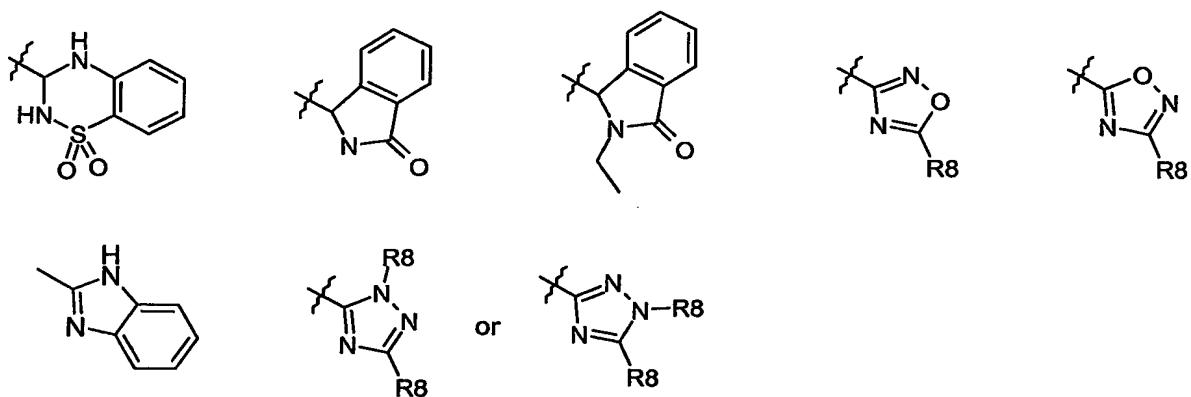


In another embodiment $-(Y)_m-R^3$ and $-R^9$ combine with the nitrogen atom to which they are attached to form

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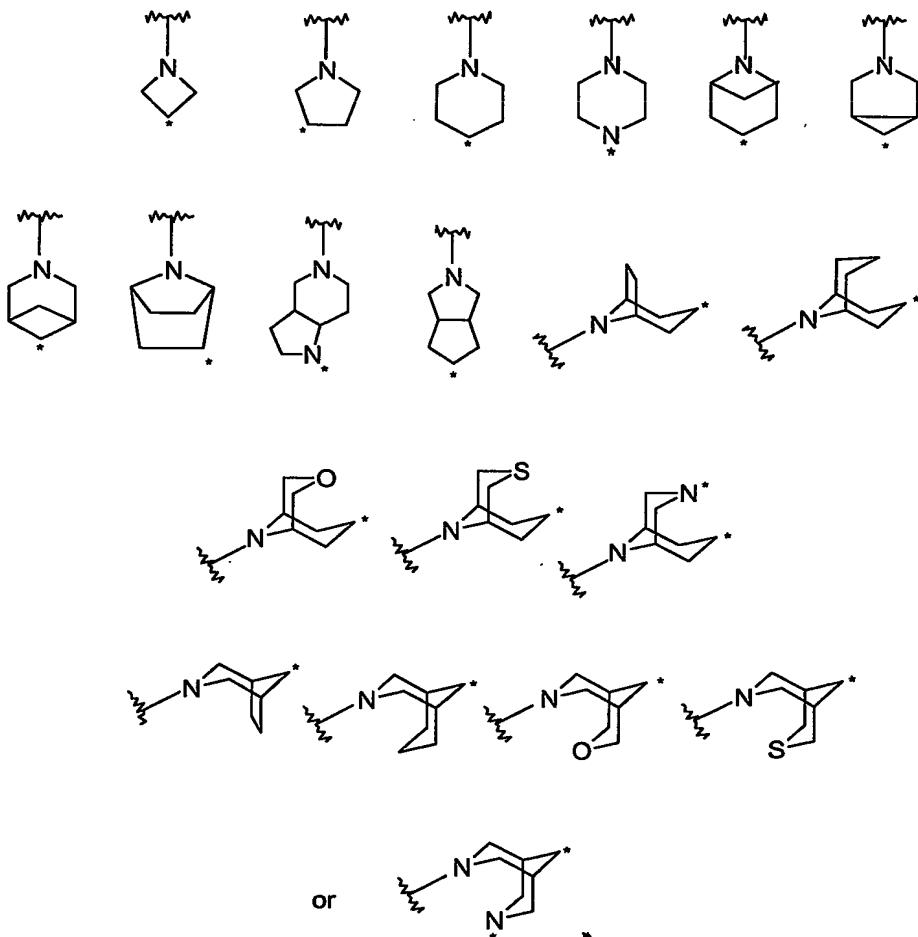
In one embodiment R^1 is selected from



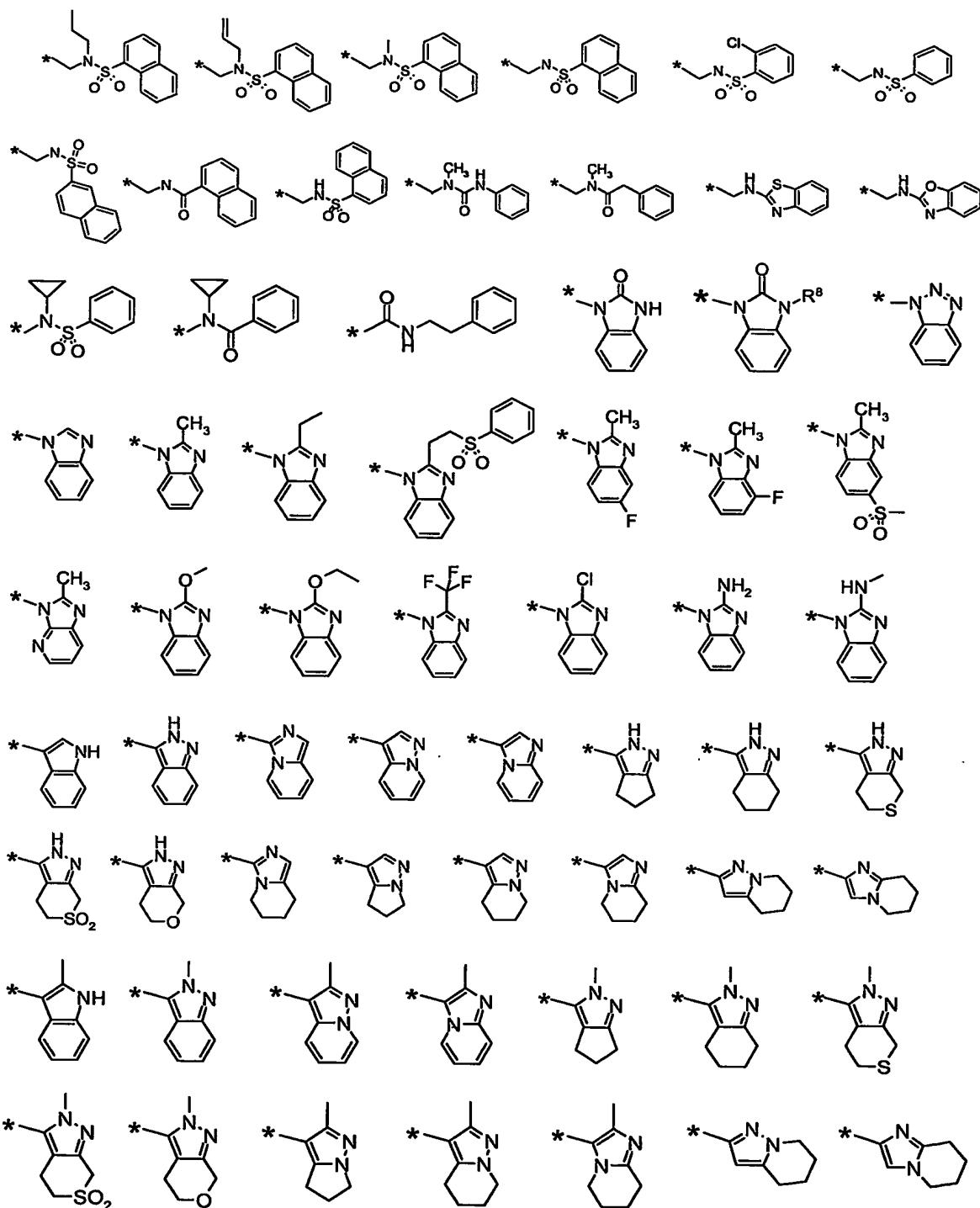
In one embodiment X is $-(\text{CH}_2)-$, $-(\text{CH}_2-\text{CH}_2)-$, or $-(\text{CH}_2-\text{CH}_2-\text{CH}_2)-$. Suitably X is optionally substituted by one or more halogen or oxo. Further X optionally has 1-3 heteroatoms selected from oxygen, phosphorus, sulfur, or nitrogen.

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In one embodiment the A ring is selected from the following, where the asterisk (*) indicates the preferred, but not limiting, point(s) of substitution:

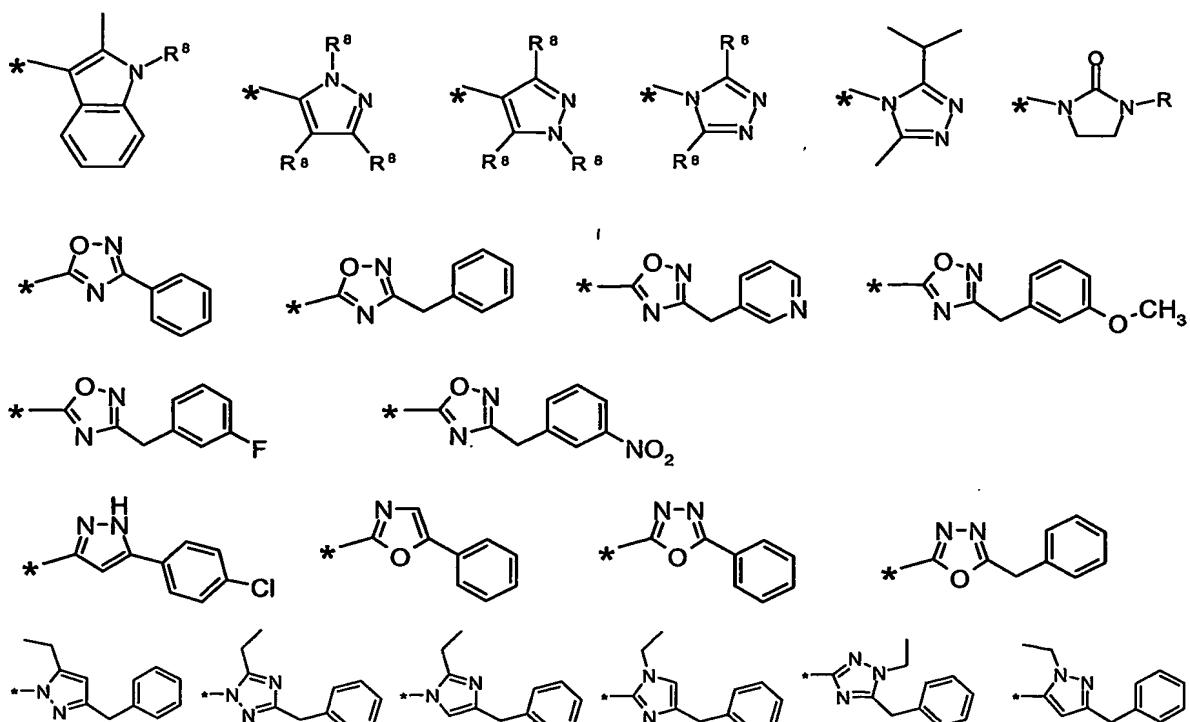


10 Suitably each R^2 , with the asterisk (*) indicating a preferred, but not limiting, point of substitution from Ring A, independently is selected from

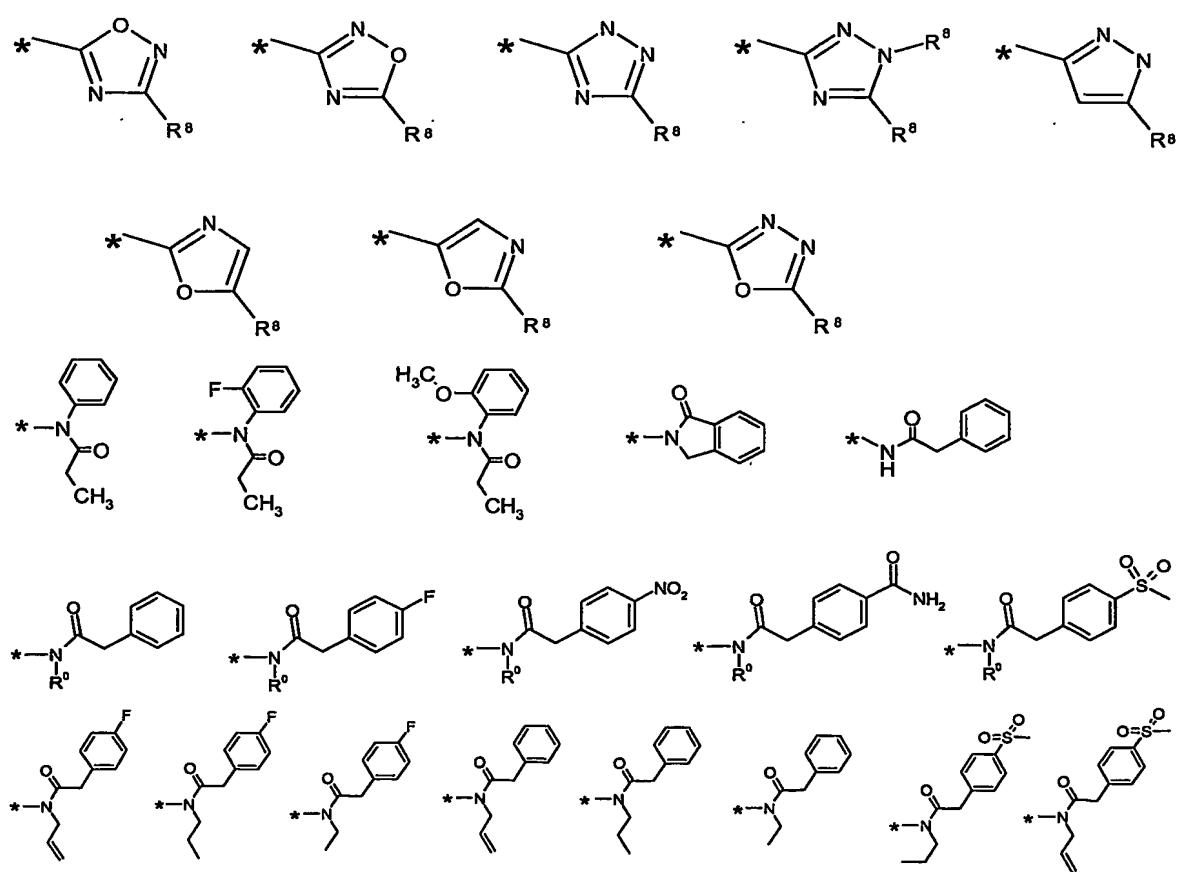


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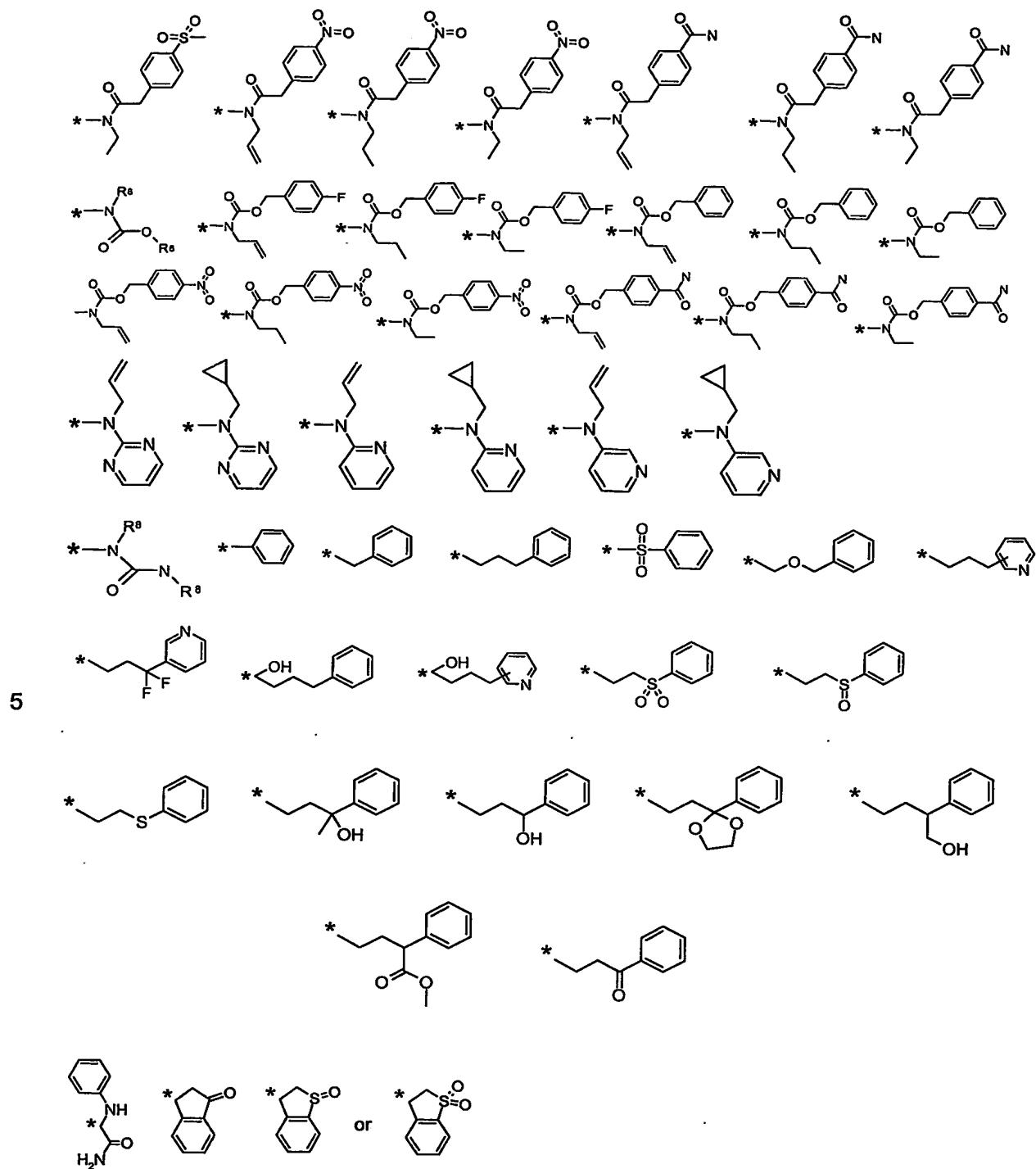
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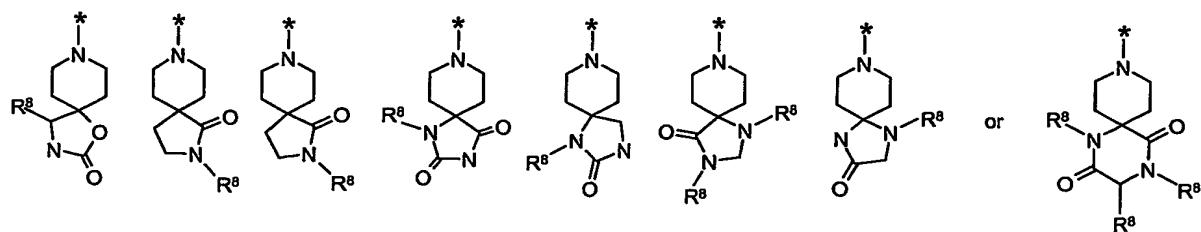


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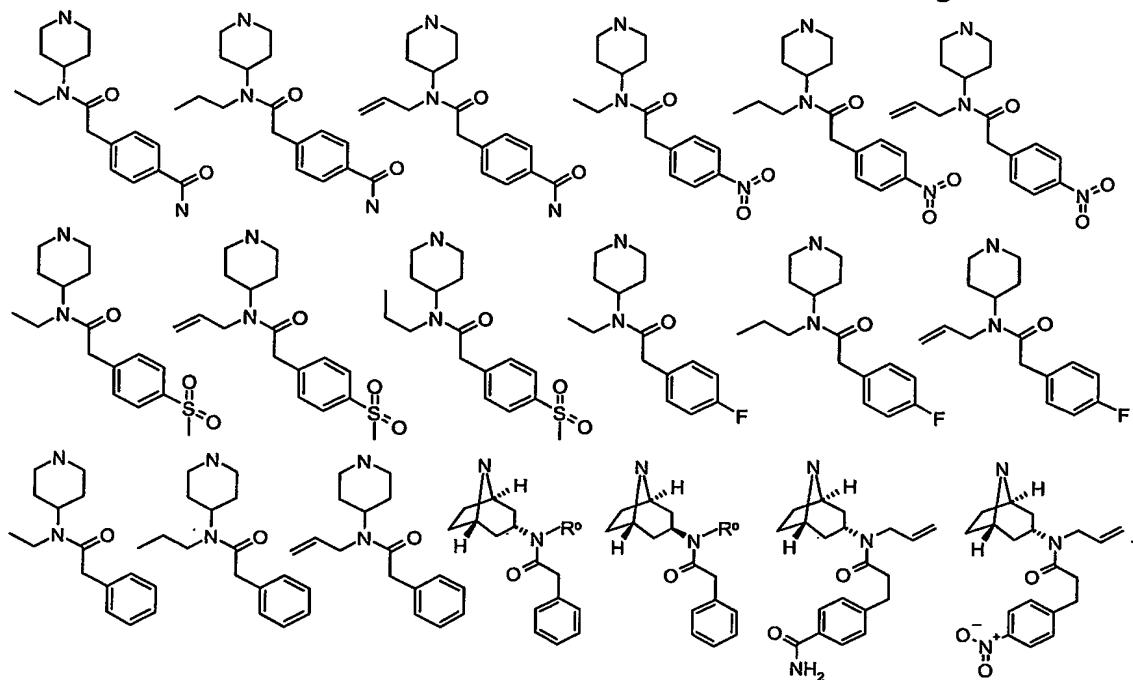


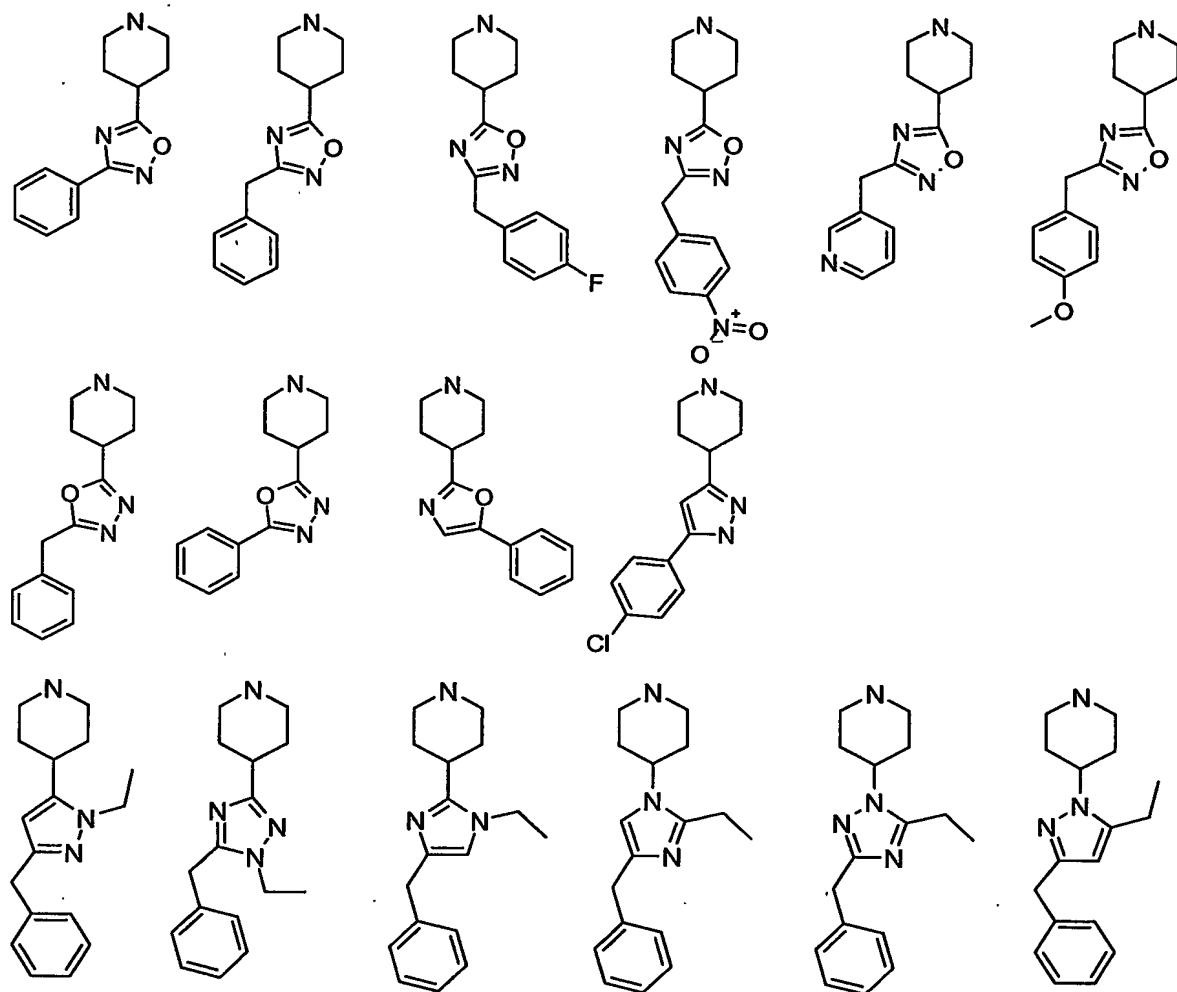
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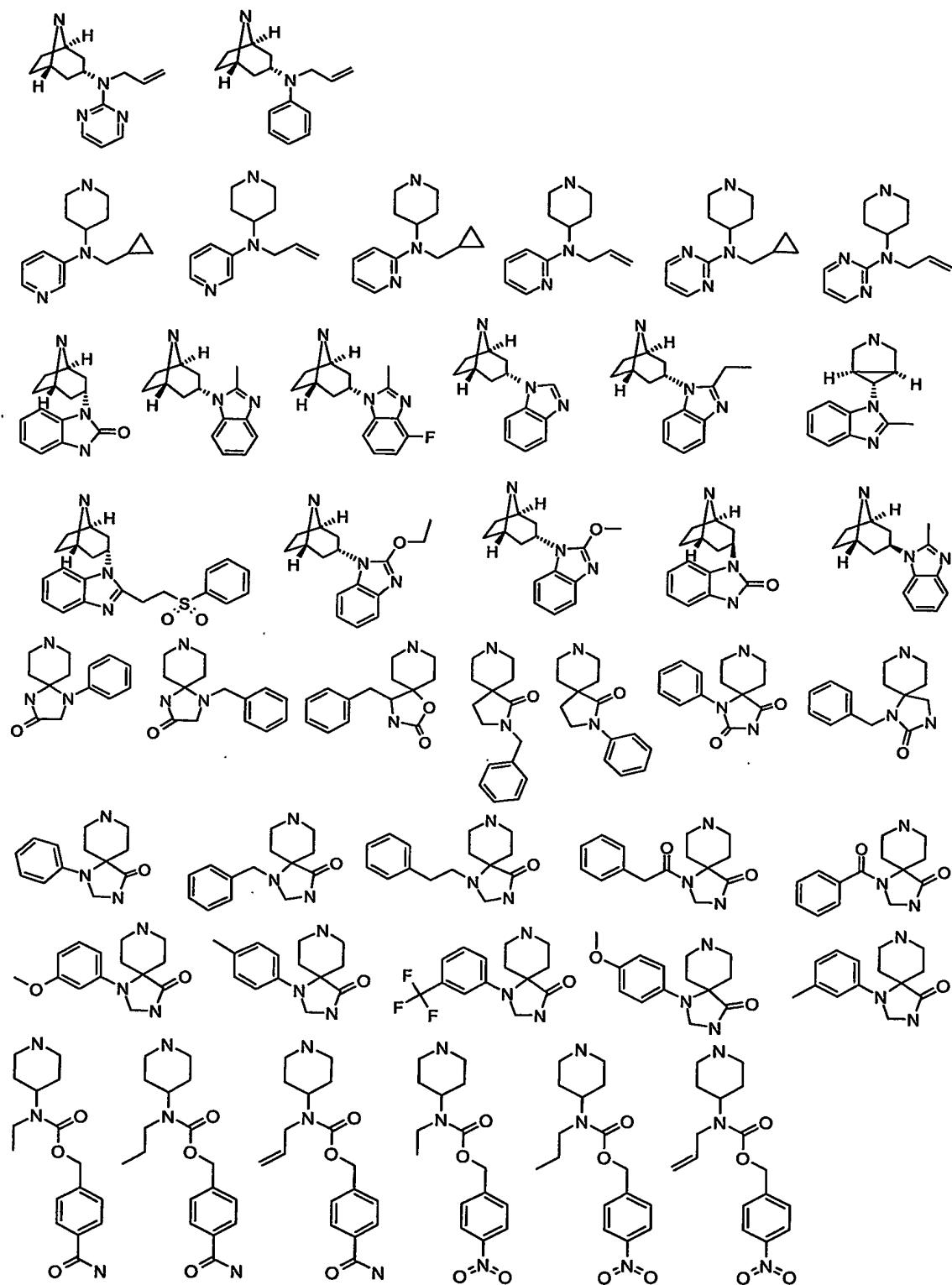
In one embodiment the ring A, with two geminal R²s, is selected from:



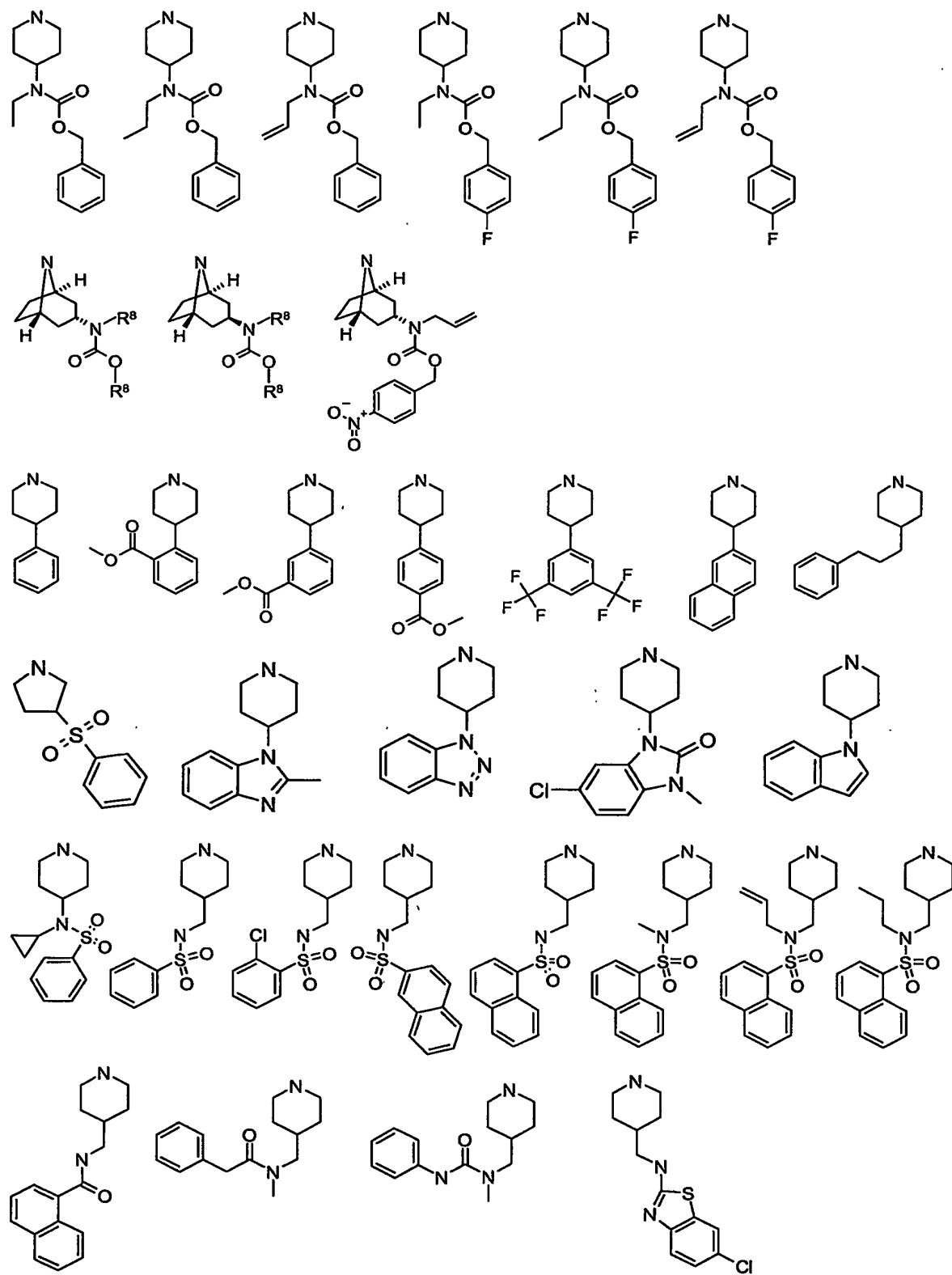
Suitably the A ring is tropane or piperidine, either optionally substituted with one or more R². Preferably, A--R² is comprised of one of the following:

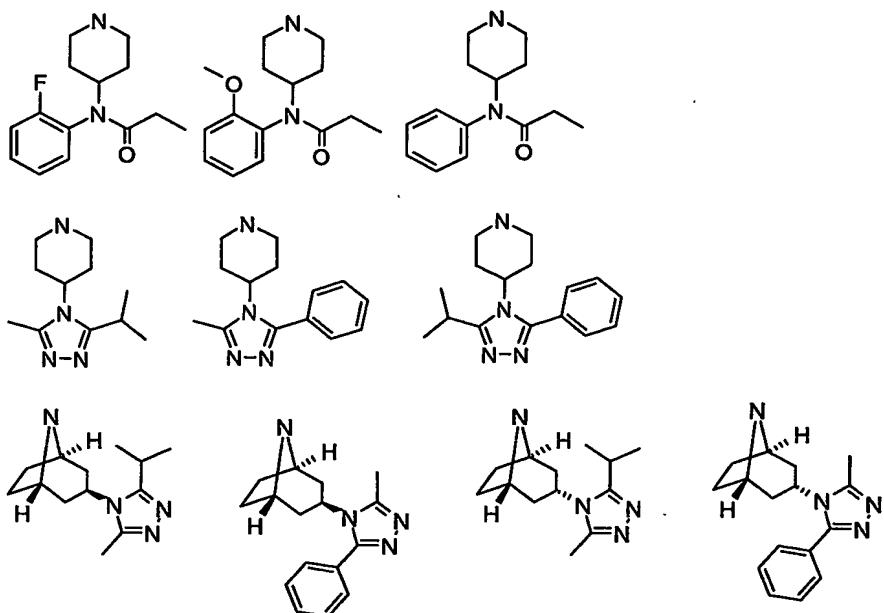






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In one embodiment the A ring contains at least one additional nitrogen atom
 5 and said A ring optionally is N-substituted. Suitably the A ring is N-substituted with
 $-(CH_2)_a-(V_b-R^+)$.

Another aspect of the present invention includes a method of treatment
 including prevention of a viral infection in a mammal comprising administering to said
 10 mammal an antiviral effective amount of a compound of the present invention.
 Preferably the viral infection is an HIV infection.

Another aspect of the present invention includes a method of treatment
 including prevention of a bacterial infection in a mammal comprising administering to
 15 said mammal an effective amount of a compound of the present invention.
 Preferably the bacterium is *Yersinia pestis*.

Another aspect of the present invention includes a method of treatment
 including prevention of multiple sclerosis, rheumatoid arthritis, autoimmune diabetes,
 20 chronic implant rejection, asthma, rheumatoid arthritis, Crohns Disease, inflammatory
 bowel disease, chronic inflammatory disease, glomerular disease, nephrotoxic serum
 nephritis, kidney disease, Alzheimer's Disease , autoimmune encephalomyelitis,
 arterial thrombosis, allergic rhinitis, arteriosclerosis, Sjogren's syndrome
 (dermatomyositis), systemic lupus erythematosus, graft rejection, cancers with
 25 leukocyte infiltration of the skin or organs, infectious disorders including bubonic and

pneumonic plague, human papilloma virus infection, prostate cancer, wound healing, amyotrophic lateral sclerosis and immune mediated disorders in a mammal comprising administering to said mammal a pharmaceutically effective amount of a compound of the present invention.

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Another aspect of the present invention includes a compound of the present invention for use in medical therapy.

10 Another aspect of the present invention includes the use of a compound of the present invention in the manufacture of a medicament for the treatment including prophylaxis of a viral infection. Preferably the viral infection is a HIV infection.

15 Another aspect of the present invention includes the use of a compound of the present invention in the manufacture of a medicament for the treatment including prophylaxis of a bacterial infection. Preferably the bacterium is *Yersinia pestis*.

20 Another aspect of the present invention includes the use of a compound of the present invention in the manufacture of a medicament for the treatment including prophylaxis of multiple sclerosis, rheumatoid arthritis, autoimmune diabetes, chronic implant rejection, asthma, rheumatoid arthritis, Crohns Disease, inflammatory bowel disease, chronic inflammatory disease, glomerular disease, nephrotoxic serum nephritis, kidney disease, Alzheimer's Disease , autoimmune encephalomyelitis, arterial thrombosis, allergic rhinitis, arteriosclerosis, Sjogren's syndrome (dermatomyositis), systemic lupus erythematosus, graft rejection, cancers with 25 leukocyte infiltration of the skin or organs, infectious disorders including bubonic and pneumonic plague, human papilloma virus infection, prostate cancer, wound healing, amyotrophic lateral sclerosis and immune mediated disorders.

30 Another aspect of the present invention includes a pharmaceutical composition comprising a pharmaceutically effective amount of a compound of the present invention together with a pharmaceutically acceptable carrier. Preferably the pharmaceutical composition is in the form of a tablet, a capsule, or a liquid.

35 Another aspect of the present invention includes a method of treatment including prevention of a viral infection in a mammal comprising administering to said

mammal a composition comprising a compound of the present invention and another therapeutic agent. Preferably the composition comprises one or more therapeutic agent selected from the group consisting of (1-alpha, 2-beta, 3-alpha)-9-[2,3-bis(hydroxymethyl) cyclobutyl]guanine [(-)BHCG, SQ-34514, lobucavir], 9-

5 [(2R,3R,4S)-3,4-bis(hydroxymethyl)-2-oxetanoyl]adenine (oxetanocin-G), acyclic nucleosides, acyclovir, valaciclovir, famciclovir, ganciclovir, penciclovir, acyclic nucleoside phosphonates, (S)-1-(3-hydroxy-2-phosphonyl-methoxypropyl)cytosine (HPMPC), [[2-(6-amino-9H-purin-9-yl)ethoxy]methyl]phosphinylidene] bis(oxymethylene)-2,2-dimethylpropanoic acid (bis-POM PMEA, adefovir dipivoxil),

10 [[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphonic acid (tenofovir), (R)-[[2-(6-Amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphonic acid bis-(isopropoxycarbonyloxymethyl)ester (bis-POC-PMPA), ribonucleotide reductase inhibitors, 2-acetylpyridine 5-[(2-chloroanilino)thiocarbonyl] thiocarbonohydrazone and hydroxyurea, nucleoside reverse transcriptase inhibitors, 3'-azido-3'-

15 deoxythymidine (AZT, zidovudine), 2',3'-dideoxycytidine (ddC, zalcitabine), 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine (ddl, didanosine), 2',3'-didehydrothymidine (d4T, stavudine), (-)-beta-D-2,6-diaminopurine dioxolane (DAPD), 3'-azido-2',3'-dideoxythymidine-5'-H-phosphophonate (phosphonovir), 2'-deoxy-5-iodo-uridine (idoxuridine), (-)-cis-1-(2-hydroxymethyl)-1,3-oxathiolane 5-yl)-cytosine (lamivudine),

20 cis-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-5-fluorocytosine (FTC), 3'-deoxy-3'-fluorothymidine, 5-chloro-2',3'-dideoxy-3'-fluorouridine, (-)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol (abacavir), 9-[4-hydroxy-2-(hydroxymethyl)but-1-yl]-guanine (H2G), ABT-606 (2HM-H2G) ribavirin, protease inhibitors, indinavir, ritonavir, neffinavir, amprenavir, saquinavir,

25 fosamprenavir, (R)-N-tert-butyl-3-[(2S,3S)-2-hydroxy-3-N-[(R)-2-N-(isoquinolin-5-yloxyacetyl)amino-3-methylthiopropanoyl]amino-4-phenylbutanoyl]-5,5- dimethyl-1,3-thiazolidine-4-carboxamide (KNI-272), 4R-(4alpha,5alpha,6beta)]-1,3-bis[(3-aminophenyl)methyl]hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-2H-1,3-diazepin-2-one dimethanesulfonate (mozenavir), 3-[1-[3-[2-(5-

30 trifluoromethylpyridinyl)-sulfonylamino]phenyl]propyl]-4- hydroxy-6alpha-phenethyl-6beta-propyl-5,6-dihydro-2-pyranone (tipranavir), N'-[2(S)-Hydroxy-3(S)-[N-(methoxycarbonyl)-l-tert-leucylamino]-4- phenylbutyl-N alpha-(methoxycarbonyl)-N'-[4-(2-pyridyl)benzyl]-L- tert-leucylhydrazide (BMS-232632), 3-(2(S)-Hydroxy-3(S)-(3-hydroxy-2-methylbenzamido)-4-phenylbutanoyl)-5,5-dimethyl-N-(2-

35 methylbenzyl)thiazolidine-4(R)-carboxamide (AG-1776), N-(2(R)-hydroxy-1(S)-

indanyl)-2(R)-phenyl-methyl-4(S)-hydroxy-5-(1-(1-(4-benzo[b]furanylmethyl)-2(S)-N¹-(tert-butylcarboxamido)piperazinyl)pentanamide (MK-944A), interferons, α -interferon, renal excretion inhibitors, probenecid, nucleoside transport inhibitors, dipyridamole, pentoxifylline, N-acetylcysteine (NAC), Procysteine, α -trichosanthin,

5 phosphonoformic acid, immunomodulators, interleukin II, thymosin, granulocyte macrophage colony stimulating factors, erythropoetin, soluble CD₄ and genetically engineered derivatives thereof, non-nucleoside reverse transcriptase inhibitors (NNRTIs), nevirapine (BI-RG-587), alpha-((2-acetyl-5-methylphenyl)amino)-2,6-dichloro-benzeneacetamide (loviride), 1-[3-(isopropylamino)-2-pyridyl]-4-[5-

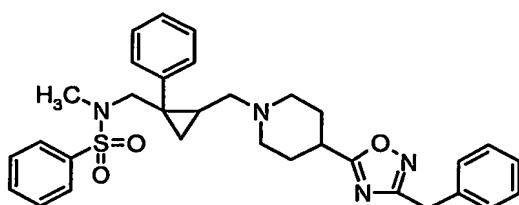
10 (methanesulfonamido)-1H-indol-2-ylcarbonyl]piperazine monomethanesulfonate (delavirdine), (10R, 11S, 12S)-12-hydroxy-6, 6, 10, 11-tetramethyl-4-propyl-11,12-dihydro-2H, 6H, 10H-benzo(1, 2-b:3, 4-b':5, 6-b")tropyran-2-one ((+) calanolide A), (4S)-6-Chloro-4-[1E]-cyclopropylethenyl)-3,4- dihydro-4-(trifluoromethyl)-2(1H)-quinazolinone (DPC-083), (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-

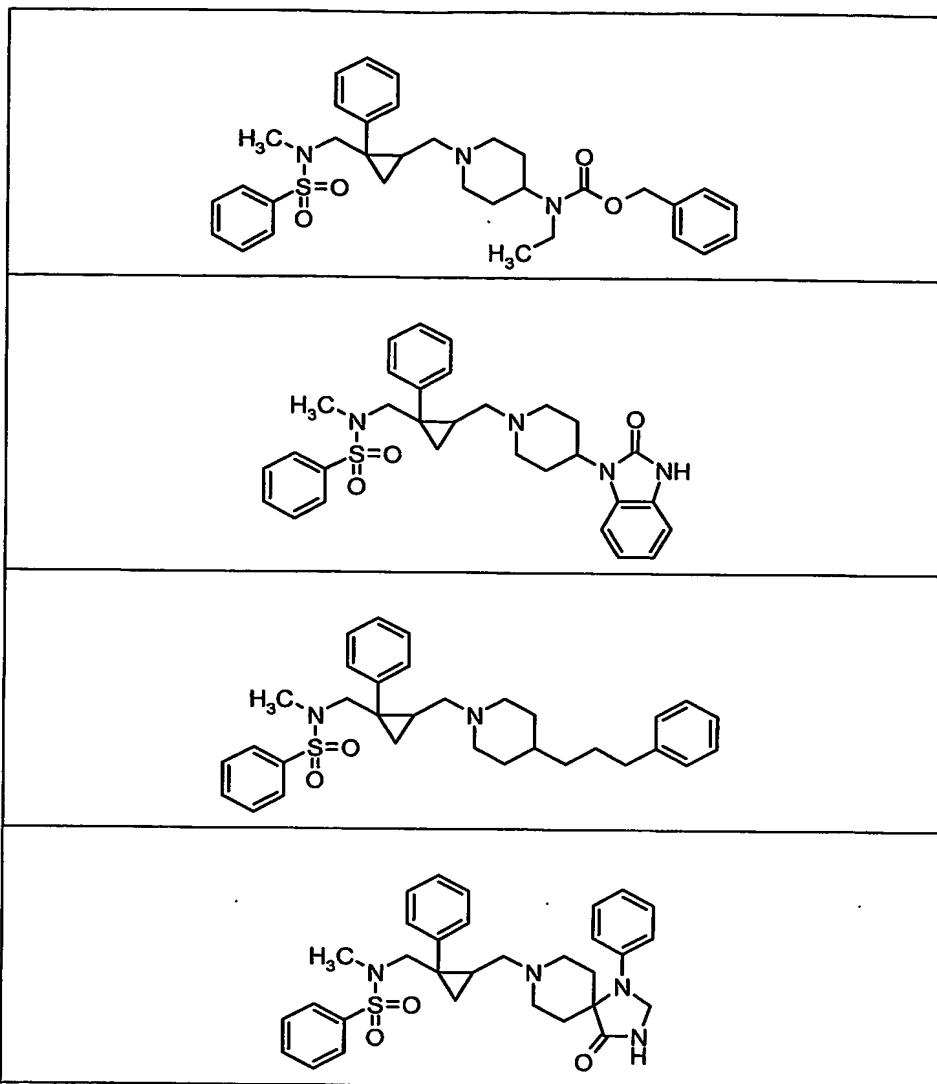
15 (trifluoromethyl)-2H-3,1-benzoxazin-2-one (efavirenz, DMP 266), 1-(ethoxymethyl)-5-(1-methylethyl)-6-(phenylmethyl)-2,4(1H,3H)-pyrimidinedione (MKC-442), and 5-(3,5-dichlorophenyl)thio-4-isopropyl-1-(4-pyridyl)methyl-1H-imidazol-2-ylmethyl carbamate (capravirine), glycoprotein 120 antagonists, PRO-2000, PRO-542, 1,4-bis[3-[(2, 4- dichlorophenyl)carbonylamino]-2-oxo-5,8-disodiumsulfanyl]naphthalyl-2,

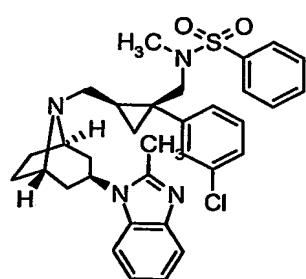
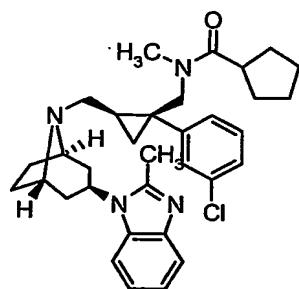
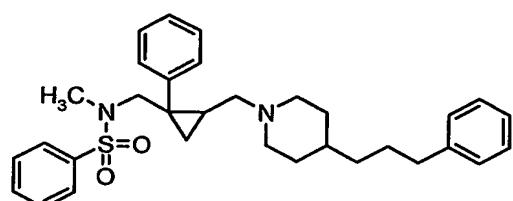
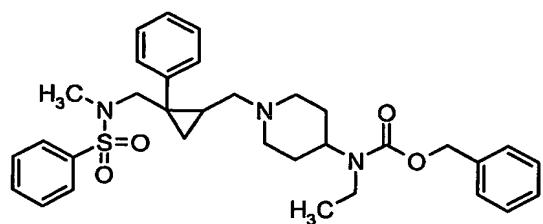
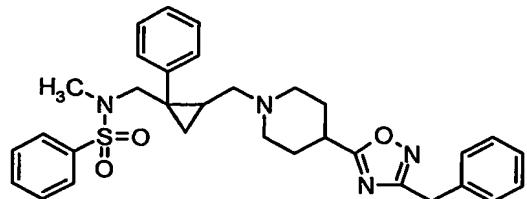
20 5-dimethoxyphenyl-1, 4-dihydrazone (FP-21399), cytokine antagonists, reticulose (Product-R), 1,1'-azobis-formamide (ADA), 1,11-(1,4-phenylenebis(methylene))bis-1,4,8,11-tetraazacyclotetradecane octahydrochloride (AMD-3100), integrase inhibitors, and fusion inhibitors.

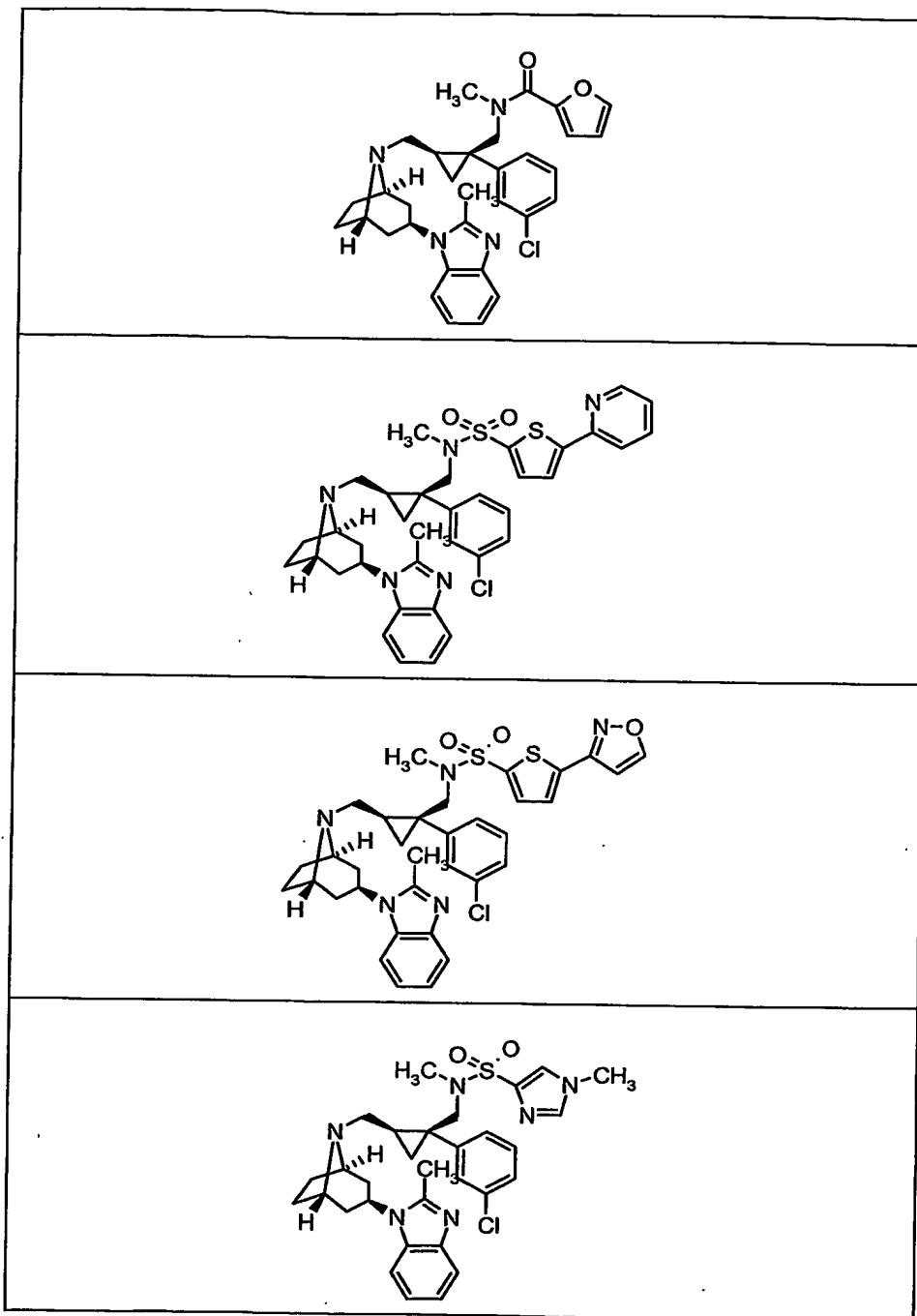
25 Another aspect of the present invention includes a method of treatment or prevention of a viral infection in a mammal comprising administering to said mammal a composition comprising a compound of the present invention and ritonavir.

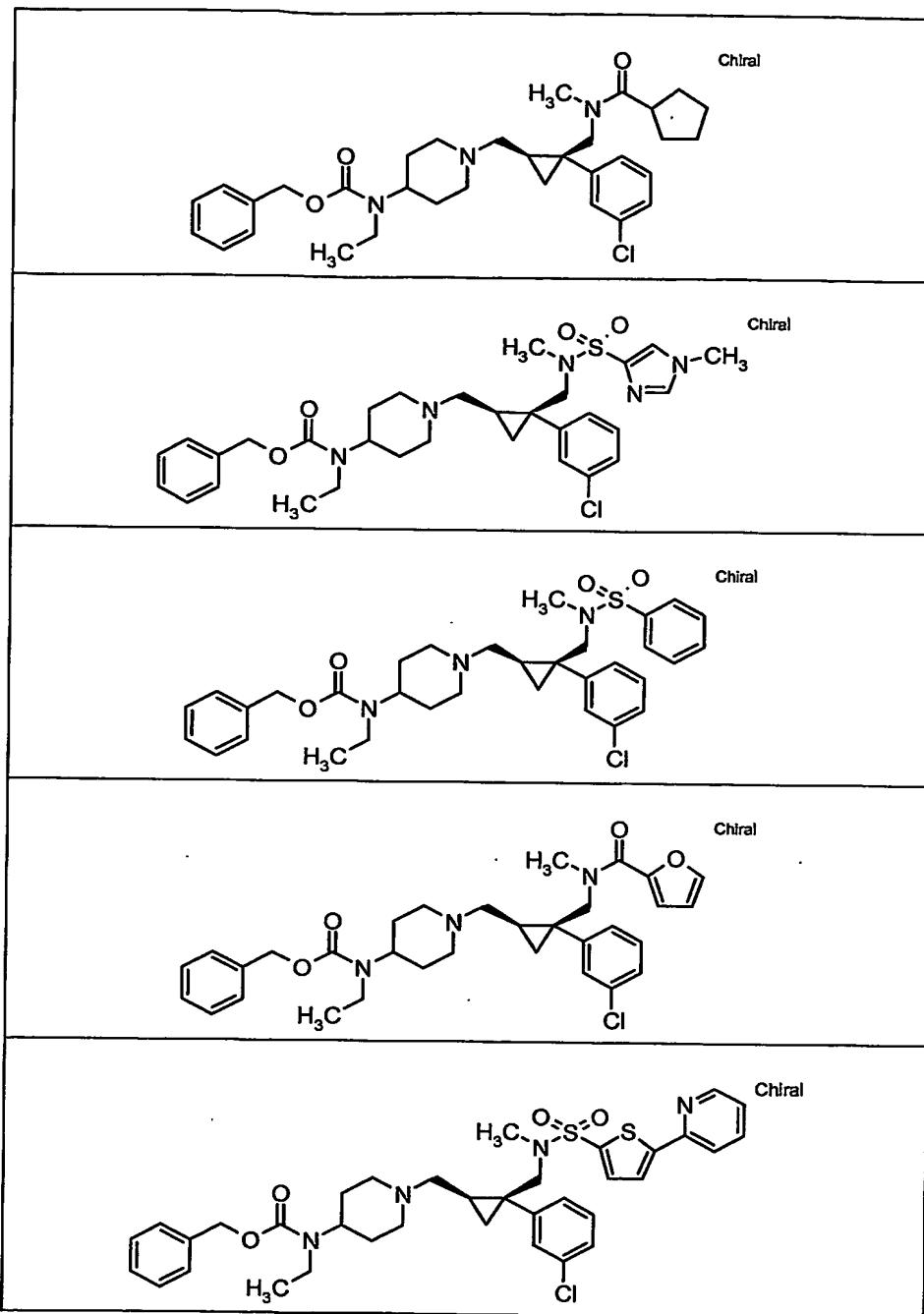
Particular compounds of the present invention include:

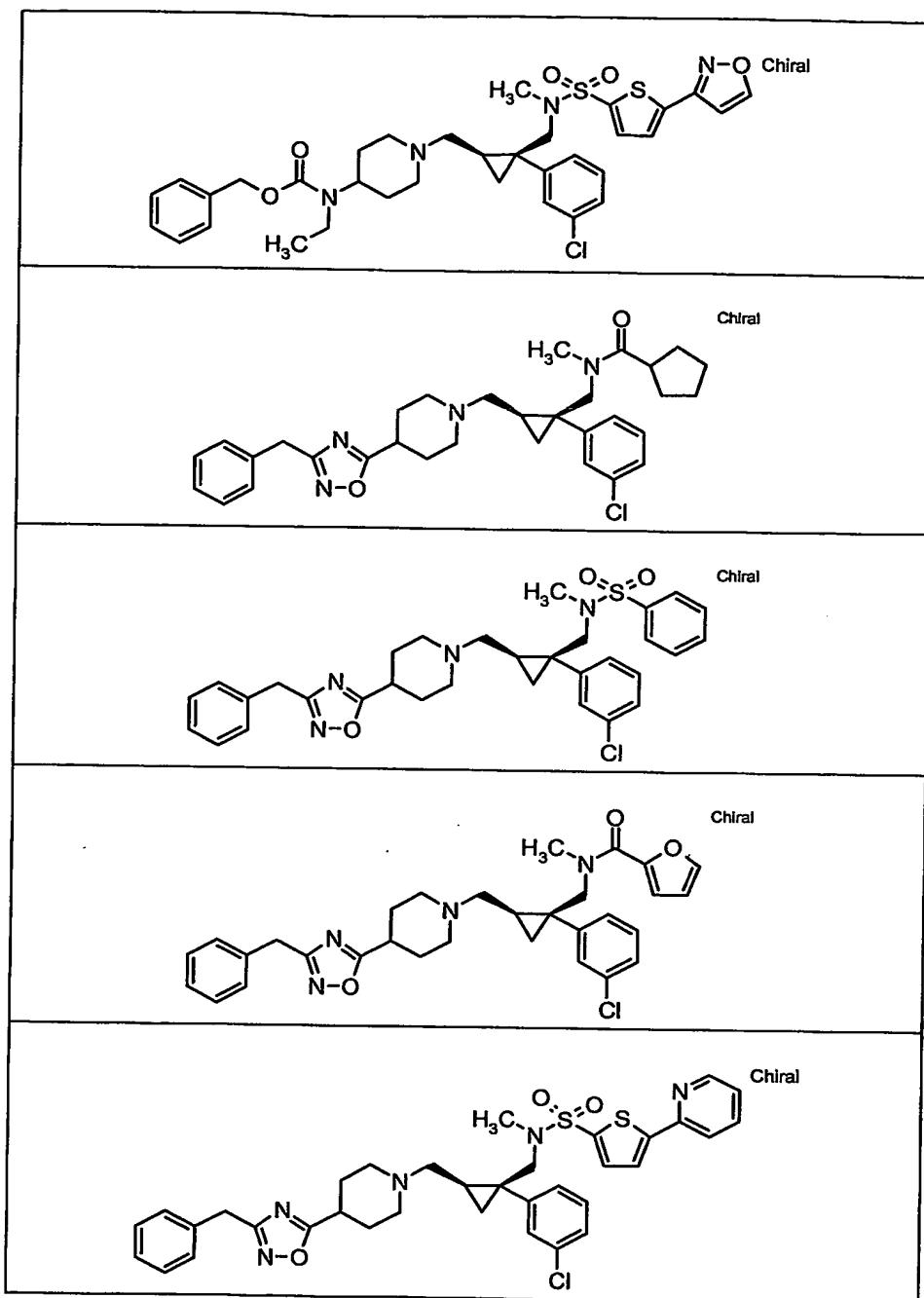


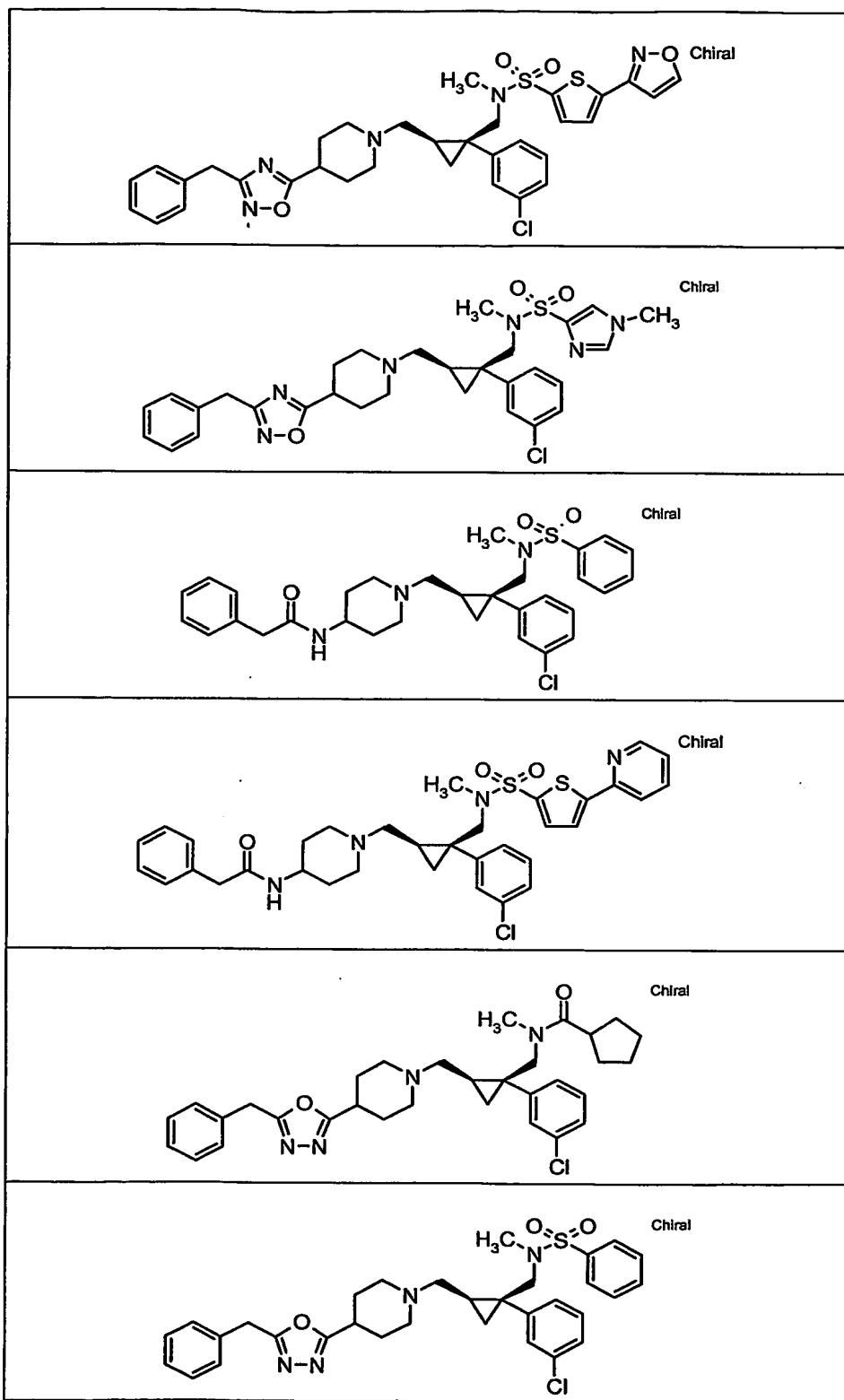


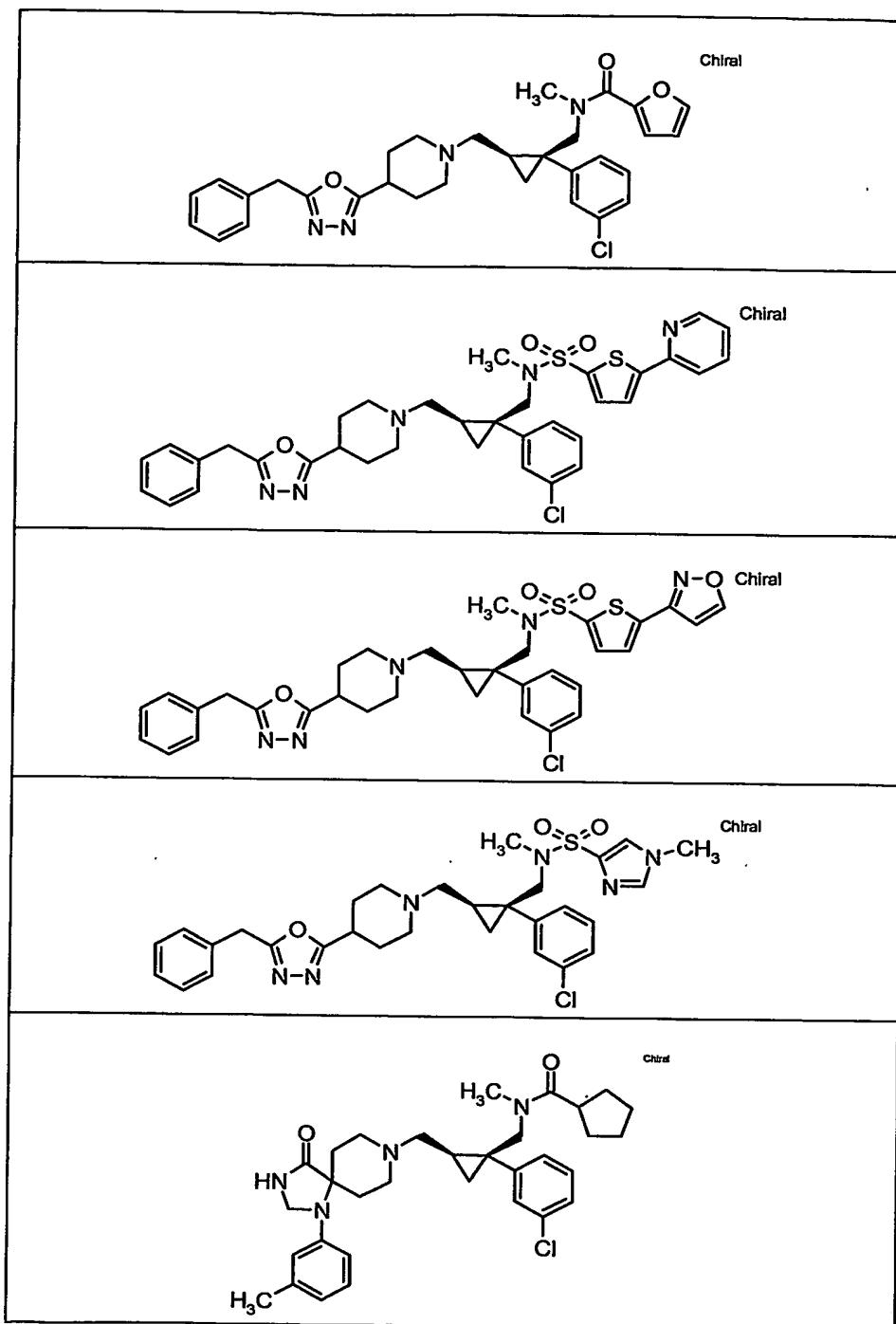


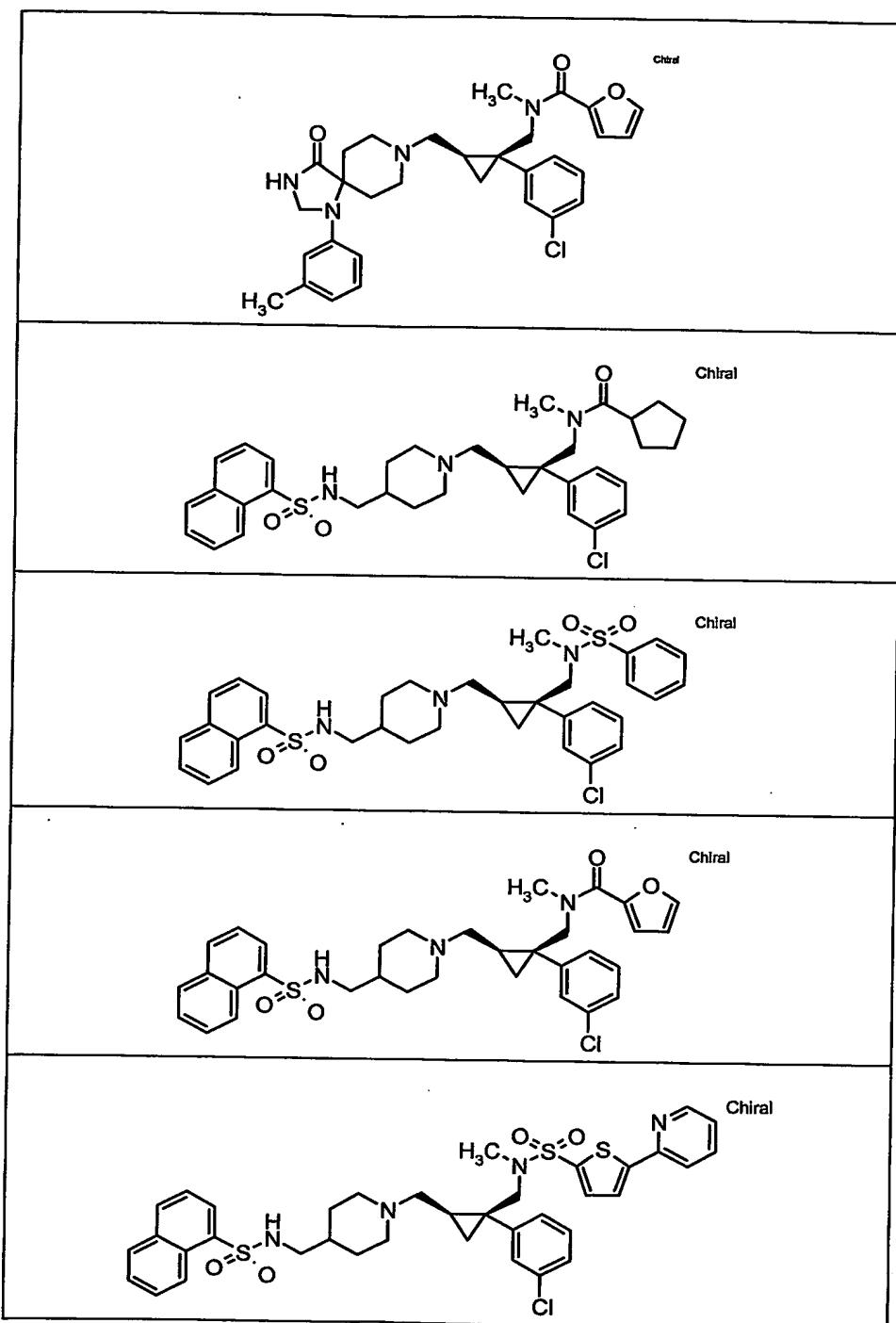


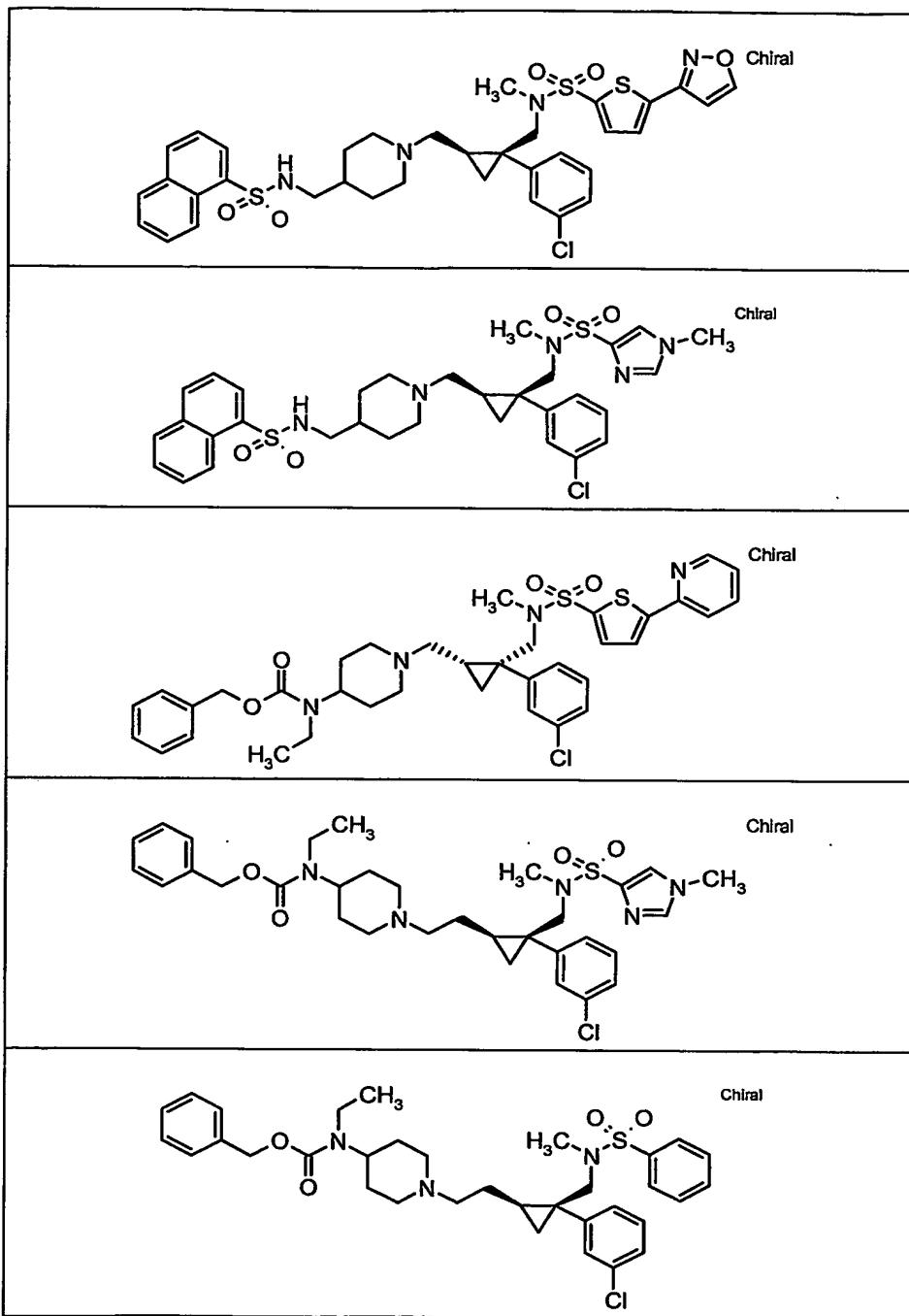


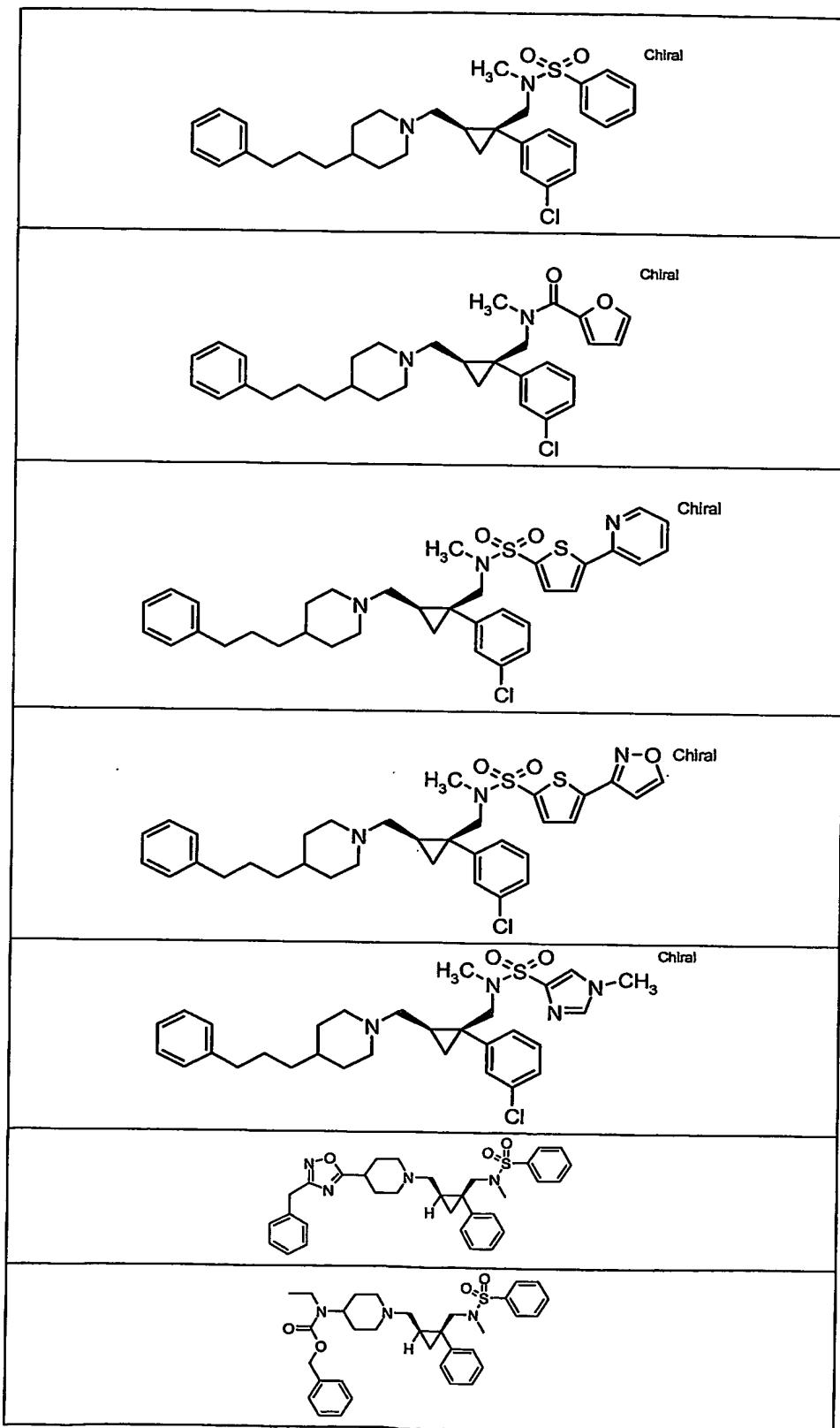


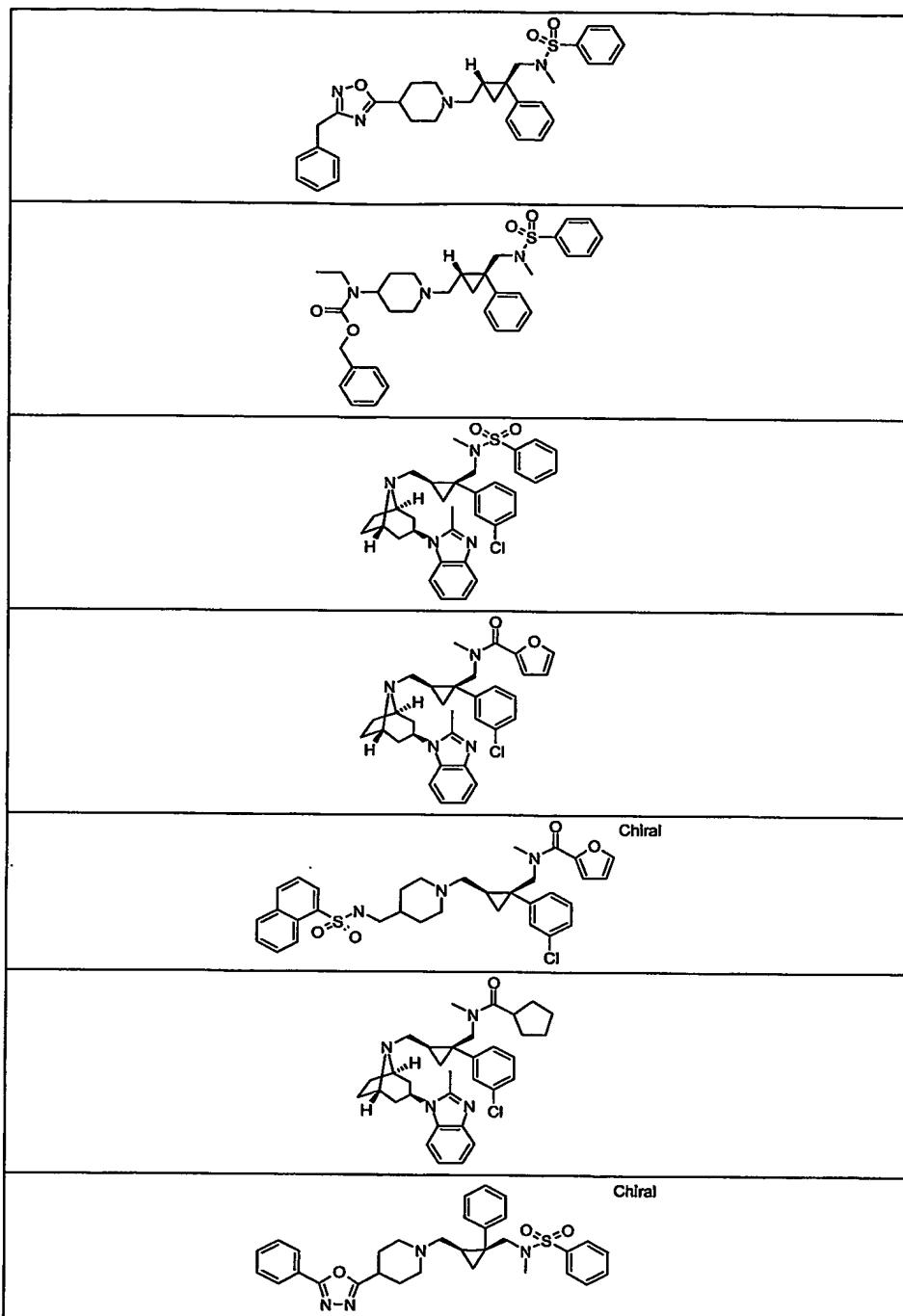












DETAILED DESCRIPTION OF THE INVENTION

The phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted" or with the term "(un)substituted." Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and each substitution is independent of the other.

The term "alkyl", alone or in combination with any other term, refers to a straight-chain or branched-chain saturated aliphatic hydrocarbon radical containing the specified number of carbon atoms. Examples of alkyl radicals include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, 5 pentyl, isoamyl, n-hexyl and the like.

The term "cycloalkyl", "carbocylyl", "carbocyclic", or "carbocycle", or "carbocyclo", alone or in combination with any other term, refers to a monocyclic or polycyclic non-aromatic hydrocarbon ring radical having three to twenty carbon 10 atoms, preferably from three to twelve carbon atoms, and more preferably from three to ten carbon atoms. If polycyclic, each ring in a carbocylyl radical is non-aromatic unless otherwise indicated. A carbocylyl radical is either completely saturated or contains one or more units of unsaturation but is not aromatic. The unsaturation, if present, may occur in any point in the ring that may result in any chemically stable 15 configuration. The term "cycloalkyl", "carbocylyl", "carbocyclic", or "carbocycle", or "carbocyclo" also includes hydrocarbon rings that are fused to one or more aromatic rings, such as in tetrahydronaphthyl, where the radical or point of attachment is on the non-aromatic ring.

20 Unless otherwise indicated, the term "cycloalkyl", "carbocylyl", "carbocyclic", or "carbocycle", or "carbocyclo" also includes each possible positional isomer of a non-aromatic hydrocarbon radical, such as in 1-decahydronaphthyl, 2-decahydronaphthyl, 1-tetrahydronaphthyl and 2-tetrahydronaphthyl. Examples of suitable cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, 25 cyclopentyl, cyclohexyl, cyclohexenyl, decahydronaphthyl, tetrahydronaphthyl and the like.

The term "alkenyl," alone or in combination with any other term, refers to a straight-chain or branched-chain alkyl group with at least one carbon-carbon double 30 bond. Examples of alkenyl radicals include, but are not limited to, ethenyl, propenyl, isopropenyl, butenyl, isobut enyl, pentenyl, hexenyl, hexadienyl and the like.

The term "alkynyl" refers to hydrocarbon groups of either a straight or branched configuration with one or more carbon-carbon triple bonds which may

occur in any stable point along the chain, such as ethynyl, propynyl, butynyl, pentynyl, and the like.

The term "alkoxy" refers to an alkyl ether radical, wherein the term "alkyl" is defined above. Examples of suitable alkyl ether radicals include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like.

The term "aryl", alone or in combination with any other term, refers to an aromatic monocyclic or polycyclic hydrocarbon ring radical containing five to twenty carbon atoms, preferably from six to fourteen carbon atoms, and more preferably from six to ten carbon atoms. Also included within the scope of the term "aryl", as it is used herein, is a group in which an aromatic hydrocarbon ring is fused to one or more non-aromatic carbocyclic or heteroatom-containing rings, such as in an indanyl, phenanthridinyl or tetrahydronaphthyl, where the radical or point of attachment is on the aromatic hydrocarbon ring.

Unless otherwise indicated, the term "aryl" also includes each possible positional isomer of an aromatic hydrocarbon radical, such as in 1-naphthyl, 2-naphthyl, 5-tetrahydronaphthyl, 6-tetrahydronaphthyl, 1-phenanthridinyl, 2-phenanthridinyl, 3-phenanthridinyl, 4-phenanthridinyl, 7-phenanthridinyl, 8-phenanthridinyl, 9-phenanthridinyl and 10-phenanthridinyl. Examples of aryl radicals include, but are not limited to, phenyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, phenanthrenyl, tetrahydronaphthyl, indanyl, phenanthridinyl and the like.

The term "aralkyl" further refers to groups of -R_aR_b, where R_a is an alkylene as defined herein and R_b is an aryl as defined herein.

The term "heterocycle", "heterocyclic", and "heterocycl", alone or in combination with any other term, refers to a non-aromatic monocyclic or polycyclic ring radical containing three to twenty carbon atoms, preferably three to seven carbon atoms if monocyclic and eight to eleven carbon atoms if bicyclic, and in which one or more ring carbons, preferably one to four, are each replaced by a heteroatom such as N, O, and S. If polycyclic, each ring in a heterocycl radical is non-aromatic unless otherwise indicated. A heterocyclic ring may be fully saturated or may contain

one or more units of unsaturation but is not aromatic. The unsaturation, if present, may occur in any point in the ring that may result in any chemically stable configuration. The heterocyclic ring may be attached at a carbon or heteroatom that results in the creation of a stable structure. Preferred heterocycles include 5-7 5 membered monocyclic heterocycles and 8-10 membered bicyclic heterocycles.

Also included within the scope of the term "heterocycle", "heterocyclic", or "heterocyclyl" is a group in which a non-aromatic heteroatom-containing ring is fused to one or more aromatic rings, such as in an indolinyl, chromanyl, phenanthridinyl or 10 tetrahydroquinolinyl, where the radical or point of attachment is on the non-aromatic heteroatom-containing ring. Unless otherwise indicated, the term "heterocycle", "heterocyclic", or "heterocyclyl" also includes each possible positional isomer of a heterocyclic radical, such as in 1-decahydroquinoline, 2-decahydroquinoline, 3-decahydroquinoline, 4-decahydroquinoline, 5-decahydroquinoline, 6-decahydroquinoline, 7-decahydroquinoline, 7-decahydroquinoline, 8-decahydroquinoline, 4a-decahydroquinoline, 8a-decahydroquinoline, 1-indolinyl, 2-indolinyl, 3-indolinyl, 1-tetrahydroquinoline, 2-tetrahydroquinoline, 3-tetrahydroquinoline and 4-tetrahydroquinoline. The term "heterocyclalkyl" refers to an alkyl group substituted by a heterocyclyl.

20

Examples of heterocyclic groups include, but are not limited to, imidazolinyl, 2,3-dihydro-1H-imidazolyl, imidazolidinyl, indazolinolyl, perhydropyridazyl, pyrrolinyl, pyrrolidinyl, 4H-pyrazolyl, piperidinyl, pyranyl, pyrazolinyl, piperazinyl, morpholinyl, thiamorpholinyl, thiazolidinyl, thiamorpholinyl, oxopiperidinyl, oxopyrrolidinyl, 25 azepinyl, tetrahydrofuranyl, oxoazepinyl, tetrahydropyranyl, thiazolyl, dioxolyl, dioxinyl, oxathiolyl, benzodioxolyl, dithioly, dithiolanyl, tetrahydrothiophenyl, sulfolanyl, dioxanyl, dioxolanyl, tetrahydrofurodihydrofuranyl, dihydropyranyl, tetrahydropyranodihydrofuranyl, tetracyclicfurofuran, tetrahydropyranofuranyl, diazolonyl, phthalimidinyl, benzoxanyl, benzopyrrolidinyl, benzopiperidinyl, 30 benzoxolanyl, benzothiolanyl and benzothianyl.

The term "heteroaryl", alone or in combination with any other term, refers to an aromatic monocyclic or polycyclic ring radical containing five to twenty carbon atoms, preferably five to ten carbon atoms, in which one or more ring carbons, 35 preferably one to four, are each replaced by a heteroatom such as N, O, and S.

Preferred heteroaryl groups include 5-6 membered monocyclic heteroaryls and 8-10 membered bicyclic heteroaryls.

Also included within the scope of the term "heteroaryl" is a group in which a heteroaromatic ring is fused to one or more aromatic or non-aromatic rings where the radical or point of attachment is on the heteroaromatic ring. Examples include, but are not limited to, pyrido[3,4-d]pyrimidinyl, 7,8-dihydro-pyrido[3,4-d]pyrimidine and 5,6,7,8-tetrahydro-pyrido[3,4-d]pyrimidine. Unless otherwise indicated, the term "heteroaryl" also includes each possible positional isomer of a heteroaryl radical, such as in 2-pyrido[3,4-d]pyrimidinyl and 4-pyrido[3,4-d]pyrimidinyl.

Examples of heteroaryl groups include, but are not limited to, imidazolyl, quinolyl, isoquinolyl, indolyl, indazolyl, pyridazyl, pyridyl, pyrrolyl, pyrazolyl, pyrazinyl, quinoxalyl, pyrimidinyl, pyridazinyl, furyl, thienyl, triazolyl, thiazolyl, carbazolyl, carbolinyl, tetrazolyl, benzofuranyl, oxazolyl, benzoxazolyl, isoxazolyl, isothiazolyl, thiadiazolyl, furazanyl, oxadiazolyl, benzimidazolyl, benzothienyl, quinolinyl, benzotriazolyl, benzothiazolyl, isoquinolinyl, isoindolyl, acridinyl and benzoisoxazolyl.

The term "heteroaralkyl" further refers to groups of -R_aR_b, where R_a is an alkylene as defined herein and R_b is a heteroaryl as defined herein.

The term "heteroatom" means nitrogen, oxygen, phosphorus, or sulfur and includes any oxidized forms thereof, including as non-limiting examples oxidized forms of nitrogen such as N(O) {N⁺-O⁻}, oxidized forms of sulfur such as S(O) and S(O)₂, and the quaternized form of any basic nitrogen.

The term "halogen" refers to fluorine, chlorine, bromine or iodine.

The term "pharmaceutically effective amount" refers to an amount of a compound of the invention that is effective in treating a CCR5-related disease, for example a virus infection, for example an HIV infection, in a patient either as monotherapy or in combination with other agents. The term "treatment" as used herein refers to the alleviation of symptoms of a particular disorder in a patient, or the improvement of an ascertainable measurement associated with a particular disorder, and may include the suppression of symptom recurrence in an asymptomatic patient.

such as a patient in whom a viral infection has become latent. The term "prophylaxis" refers to preventing a disease or condition or preventing the occurrence of symptoms of such a disease or condition, in a patient. As used herein, the term "patient" refers to a mammal, including a human.

5

The term "pharmaceutically acceptable carrier" refers to a carrier that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the therapeutic agent.

10

The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an inhibitorily active metabolite or residue thereof. Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species.

25 Pharmaceutically acceptable salts of the compounds according to the invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicyclic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as 30 intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

35 Salts derived from appropriate bases include alkali metal (e.g. sodium), alkaline earth metal (e.g., magnesium), ammonium, NW_4^+ (wherein W is C_{1-4} alkyl) and other amine salts. Physiologically acceptable salts of a hydrogen atom or an

amino group include salts of organic carboxylic acids such as acetic, lactic, tartaric, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids and inorganic acids such as hydrochloric, sulfuric, phosphoric and sulfamic acids.

5 Physiologically acceptable salts of a compound with a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ , NH_4^+ , and NW_4^+ (wherein W is a C_{1-4} alkyl group).

10 Any reference to any of the above compounds also includes a reference to a pharmaceutically acceptable salt thereof.

15 Salts of the compounds of the present invention may be made by methods known to a person skilled in the art. For example, treatment of a compound of the present invention with an appropriate base or acid in an appropriate solvent will yield the corresponding salt.

20 Esters of the compounds of the present invention are independently selected from the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxyethyl), aryl (for example, phenyl optionally substituted by, for example, halogen, C_{1-4} alkyl, or C_{1-4} alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, 25 methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol.

30 In such esters, unless otherwise specified, any alkyl moiety present advantageously contains from 1 to 18 carbon atoms, particularly from 1 to 6 carbon atoms, more particularly from 1 to 4 carbon atoms. Any cycloalkyl moiety present in such esters advantageously contains from 3 to 6 carbon atoms. Any aryl moiety present in such esters advantageously comprises a phenyl group.

The compounds according to the invention contain one or more asymmetric carbon atoms and thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereoisomers. All such isomeric forms of these compounds are expressly included in the present invention.

5 Each stereogenic carbon may be of the R or S configuration. Although the specific compounds exemplified in this application may be depicted in a particular stereochemical configuration, compounds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned.

10 Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by a ¹³C- or ¹⁴C-enriched carbon are also within the scope of this invention.

15 Certain compounds of this invention may exist in alternative tautomeric forms. All such tautomeric forms of the present compounds are within the scope of the invention. Unless otherwise indicated, the representation of either tautomer is meant to include the other.

20 The present invention features compounds according to the invention for use in medical therapy, for example for the treatment including prophylaxis of viral infections such as an HIV infections and associated conditions. Reference herein to treatment extends to prophylaxis as well as the treatment of established infections,

25 symptoms, and associated clinical conditions such as AIDS related complex (ARC), Kaposi's sarcoma, and AIDS dementia.

30 The present invention features use of the compounds of the present invention in the manufacture of a medicament for the treatment including prophylaxis of a CCR5-related disease or condition, for example, a viral infection, for example, an HIV infection.

35 According to another aspect, the present invention provides a method for the treatment including prevention of the symptoms or effects of a viral infection in an infected animal, for example, a mammal including a human, which comprises treating

said animal with a pharmaceutically effective amount of a compound according to the invention. According to one aspect of the invention, the viral infection is a retroviral infection, in particular an HIV infection. A further aspect of the invention includes a method for the treatment including prevention of the symptoms or effects of an HBV infection.

The compounds according to the invention may also be used in adjuvant therapy in the treatment of HIV infections or HIV-associated symptoms or effects, for example Kaposi's sarcoma.

10

The compounds of the present invention may also be used in the treatment including prevention of other CCR5-related diseases and conditions, including multiple sclerosis, rheumatoid arthritis, autoimmune diabetes, chronic implant rejection, asthma, rheumatoid arthritis, Crohns Disease, inflammatory bowel disease, chronic inflammatory disease, glomerular disease, nephrotoxic serum nephritis, kidney disease, Alzheimer's Disease, autoimmune encephalomyelitis, arterial thrombosis, allergic rhinitis, arteriosclerosis, Sjogren's syndrome (dermatomyositis), systemic lupus erythematosus, graft rejection, cancers with leukocyte infiltration of the skin or organs, infectious disorders including bubonic and pneumonic plague, human papilloma virus infection, prostate cancer, wound healing, amyotrophic lateral sclerosis, immune mediated disorders.

The present invention further provides a method for the treatment of a clinical condition in an animal, for example, a mammal including a human which clinical condition includes those which have been discussed hereinbefore, which comprises treating said animal with a pharmaceutically effective amount of a compound according to the invention. The present invention also includes a method for the treatment including prophylaxis of any of the aforementioned diseases or conditions.

30 In yet a further aspect, the present invention provides the use of a compound according to the invention in the manufacture of a medicament for the treatment including prophylaxis of any of the above mentioned viral infections or conditions.

35 The above compounds according to the invention and their pharmaceutically acceptable derivatives may be employed in combination with other therapeutic

agents for the treatment (including prevention) of the above infections or conditions.

Combination therapies according to the present invention comprise the administration of a compound of the present invention or a pharmaceutically acceptable derivative thereof and another pharmaceutically active agent. The active

5 ingredient(s) and pharmaceutically active agents may be administered simultaneously in either the same or different pharmaceutical compositions or sequentially in any order. The amounts of the active ingredient(s) and pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

10

Examples of such therapeutic agents include agents that are effective for the treatment of viral infections or associated conditions. Among these agents are (1-alpha, 2-beta, 3-alpha)-9-[2,3-bis(hydroxymethyl)cyclobutyl]guanine [(-)BHCG, SQ-34514, lobucavir], 9-[(2R,3R,4S)-3,4-bis(hydroxymethyl)-2-oxetanosyl]adenine

15 (oxetanocin-G), acyclic nucleosides, for example acyclovir, valaciclovir, famciclovir, ganciclovir, and penciclovir, acyclic nucleoside phosphonates, for example (S)-1-(3-hydroxy-2-phosphonyl-methoxypropyl)cytosine (HPMPC), [[2-(6-amino-9H-purin-9-yl)ethoxy]methyl]phosphinylidene]bis(oxymethylene)-2,2-dimethylpropanoic acid (bis-POM PMEA, adefovir dipivoxil), [(1R)-2-(6-amino-9H-purin-9-yl)-1-

20 methylethoxy]methyl]phosphonic acid (tenofovir), and (R)-[[2-(6-Amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphonic acid bis-(isopropoxycarbonyloxymethyl)ester (bis-POC-PMPA), ribonucleotide reductase inhibitors, for example 2-acetylpyridine 5-[(2-chloroanilino)thiocarbonyl] thiocarbonohydrazone and hydroxyurea, nucleoside reverse transcriptase inhibitors, for example 3'-azido-3'-deoxythymidine (AZT,

25 zidovudine), 2',3'-dideoxycytidine (ddC, zalcitabine), 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine (ddI, didanosine), 2',3'-didehydrothymidine (d4T, stavudine), (-)-beta-D-2,6-diaminopurine dioxolane (DAPD), 3'-azido-2',3'-dideoxythymidine-5'-H-phosphophonate (phosphonovir), 2'-deoxy-5-iodo-uridine (idoxuridine), (-)-cis-1-(2-hydroxymethyl)-1,3-oxathiolane 5-yl)-cytosine (lamivudine), cis-1-(2-

30 (hydroxymethyl)-1,3-oxathiolan-5-yl)-5-fluorocytosine (FTC), 3'-deoxy-3'-fluorothymidine, 5-chloro-2',3'-dideoxy-3'-fluorouridine, (-)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol (abacavir), 9-[4-hydroxy-2-(hydroxymethyl)but-1-yl]-guanine (H2G), ABT-606 (2HM-H2G) and ribavirin, protease inhibitors, for example indinavir, ritonavir, nelfinavir, amprenavir,

35 saquinavir, fosamprenavir, (R)-N-tert-butyl-3-[(2S,3S)-2-hydroxy-3-N-[(R)-2-N-

(isoquinolin-5-yloxyacetyl)amino-3-methylthiopropanoyl]amino-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide (KNI-272), 4R-(4alpha,5alpha,6beta)]-1,3-bis[(3-aminophenyl)methyl]hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-2H-1,3-diazepin-2-one dimethanesulfonate (mozenavir), 3-[1-[3-[2-(5-trifluoromethylpyridinyl)-sulfonylamino]phenyl]propyl]-4- hydroxy-6alpha-phenethyl-6beta-propyl-5,6-dihydro-2-pyranone (tipranavir), N'-[2(S)-Hydroxy-3(S)-[N-(methoxycarbonyl)-l-tert-leucylamino]-4- phenylbutyl-N ^{alpha}-(methoxycarbonyl)-N'-[4-(2-pyridyl)benzyl]-L- tert-leucylhydrazide (BMS-232632), 3-(2(S)-Hydroxy-3(S)-(3-hydroxy-2-methylbenzamido)-4-phenylbutanoyl)-5,5-dimethyl-N-(2-methylbenzyl)thiazolidine-4(R)-carboxamide (AG-1776), N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenyl-methyl-4(S)-hydroxy-5-(1-(1-(4-benzo[b]furanyl methyl)-2(S)-N'-(tert-butylcarboxamido)piperazinyl)pentanamide (MK-944A), interferons such as α -interferon, renal excretion inhibitors such as probenecid, nucleoside transport inhibitors such as dipyradomole; pentoxifylline, N-acetylcysteine (NAC), Procysteine, α -trichosanthin, phosphonoformic acid, as well as immunomodulators such as interleukin II or thymosin, granulocyte macrophage colony stimulating factors, erythropoetin, soluble CD₄ and genetically engineered derivatives thereof, non-nucleoside reverse transcriptase inhibitors (NNRTIs), for example nevirapine (BI-RG-587), alpha-((2-acetyl-5-methylphenyl)amino)-2,6-dichloro-benzeneacetamide (loviride), 1-[3-(isopropylamino)-2-pyridyl]-4-[5-(methanesulfonamido)-1H-indol-2-ylcarbonyl]piperazine monomethanesulfonate (delavirdine), (10R, 11S, 12S)-12-Hydroxy-6, 6, 10, 11-tetramethyl-4-propyl-11,12-dihydro-2H, 6H, 10H-benzo(1, 2-b:3, 4-b':5, 6-b'')tropyran-2-one ((+) calanolide A), (4S)-6-Chloro-4-[1E]-cyclopropylethenyl)-3,4- dihydro-4-(trifluoromethyl)-2(1H)-quinazolinone (DPC-083), (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one (efavirenz, DMP 266), 1-(ethoxymethyl)-5-(1-methylethyl)-6-(phenylmethyl)-2,4(1H,3H)-pyrimidinedione (MKC-442), and 5-(3,5-dichlorophenyl)thio-4-isopropyl-1-(4-pyridyl)methyl-1H-imidazol-2-ylmethyl carbamate (capravirine), glycoprotein 120 antagonists, for example PRO-2000, PRO-542 and 1,4-bis[3-[(2, 4- dichlorophenyl)carbonylamino]-2-oxo-5,8-disodiumsulfanyl]naphthalyl-2, 5-dimethoxyphenyl-1, 4-dihydrazone (FP-21399), cytokine antagonists, for example reticulose (Product-R), 1,1'-azobis-formamide (ADA), 1,11-(1,4-phenylenebis(methylene))bis-1,4,8,11-tetraazacyclotetradecane octahydrochloride (AMD-3100), integrase inhibitors, or fusion inhibitors, for example T-20 and T-1249.

The present invention further includes the use of a compound according to the invention in the manufacture of a medicament for simultaneous or sequential administration with at least another therapeutic agent, such as those defined
5 hereinbefore.

Compounds of the present invention may be administered with an agent known to inhibit or reduce the metabolism of compounds, for example ritonavir. Accordingly, the present invention features a method for the treatment including
10 prophylaxis of a disease as hereinbefore described by administration of a compound of the present invention in combination with a metabolic inhibitor. Such combination may be administered simultaneously or sequentially.

In general a suitable dose for each of the above-mentioned conditions will be
15 in the range of 0.01 to 250 mg per kilogram body weight of the recipient (e.g. a human) per day, preferably in the range of 0.1 to 100 mg per kilogram body weight per day and most preferably in the range 0.5 to 30 mg per kilogram body weight per day and particularly in the range 1.0 to 20 mg per kilogram body weight per day.
Unless otherwise indicated, all weights of active ingredient are calculated as the
20 parent compound of formula (I); for salts or esters thereof, the weights would be increased proportionally. The desired dose may be presented as one, two, three, four, five, six or more sub-doses administered at appropriate intervals throughout the day. In some cases the desired dose may be given on alternative days. These sub-doses may be administered in unit dosage forms, for example, containing 10 to 1000
25 mg or 50 to 500 mg, preferably 20 to 500 mg, and most preferably 50 to 400 mg of active ingredient per unit dosage form.

While it is possible for the active ingredient to be administered alone it is preferable to present it as a pharmaceutical composition. The compositions of the
30 present invention comprise at least one active ingredient, as defined above, together with one or more acceptable carriers thereof and optionally other therapeutic agents. Each carrier must be acceptable in the sense of being compatible with the other ingredients of the composition and not injurious to the patient.

Pharmaceutical compositions include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, and intravitreal) administration. The compositions may conveniently be presented in unit dosage

- 5 form and may be prepared by any methods well known in the art of pharmacy. Such methods represent a further feature of the present invention and include the step of bringing into association the active ingredients with the carrier, which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredients with liquid
- 10 carriers or finely divided solid carriers or both, and then if necessary shaping the product.

The present invention further includes a pharmaceutical composition as hereinbefore defined wherein a compound of the present invention or a

- 15 pharmaceutically acceptable derivative thereof and another therapeutic agent are presented separately from one another as a kit of parts.

Compositions suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the

- 20 recipient for a prolonged period of time. Such patches suitably contain the active compound 1) in an optionally buffered, aqueous solution or 2) dissolved and/or dispersed in an adhesive or 3) dispersed in a polymer. A suitable concentration of the active compound is about 1% to 25%, preferably about 3% to 15%. As one particular possibility, the active compound may be delivered from the patch by
- 25 electrotransport or iontophoresis as generally described in *Pharmaceutical Research* 3 (6), 318 (1986).

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, caplets, cachets or tablets each containing a predetermined amount of the active ingredients; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium starch glycollate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Molded tablets may be made by molding a mixture of the powdered compound moistened with an inert liquid diluent in a suitable machine. The tablets may optionally be coated or scored and may be formulated so

5 as to provide slow or controlled release of the active ingredients therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

10

15 Pharmaceutical compositions suitable for topical administration in the mouth include lozenges comprising the active ingredients in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

20

Pharmaceutical compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray. Pharmaceutical compositions containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

25

Pharmaceutical compositions for rectal administration may be presented as a suppository with a suitable carrier comprising, for example, cocoa butter or a salicylate or other materials commonly used in the art. The suppositories may be conveniently formed by admixture of the active combination with the softened or

30 melted carrier(s) followed by chilling and shaping in molds.

35 Pharmaceutical compositions suitable for parenteral administration include aqueous and nonaqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the pharmaceutical composition isotonic with the blood of the intended recipient; and aqueous and non-

aqueous sterile suspensions which may include suspending agents and thickening agents; and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The pharmaceutical compositions may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

5
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Unit dosage pharmaceutical compositions include those containing a daily dose or daily subdose of the active ingredients, as hereinbefore recited, or an appropriate fraction thereof.

15
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It should be understood that in addition to the ingredients particularly mentioned above the pharmaceutical compositions of this invention may include other agents conventional in the art having regard to the type of pharmaceutical composition in question, for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and flavoring agents.

EXAMPLES

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way.

25
30

Low resolution, open-access LC-MS data were acquired in either ESI pos/neg or APCI pos/neg mode with scanning from 100-1100 amu @ 0.5 sec/scan. LC conditions: flowrate 0.8 mL/min. 85% H₂O (0.1% formic acid) to 100% MeOH (0.075% formic acid) in 6 minutes. Phenomenex Max-RP column, 2.0x50 mm.

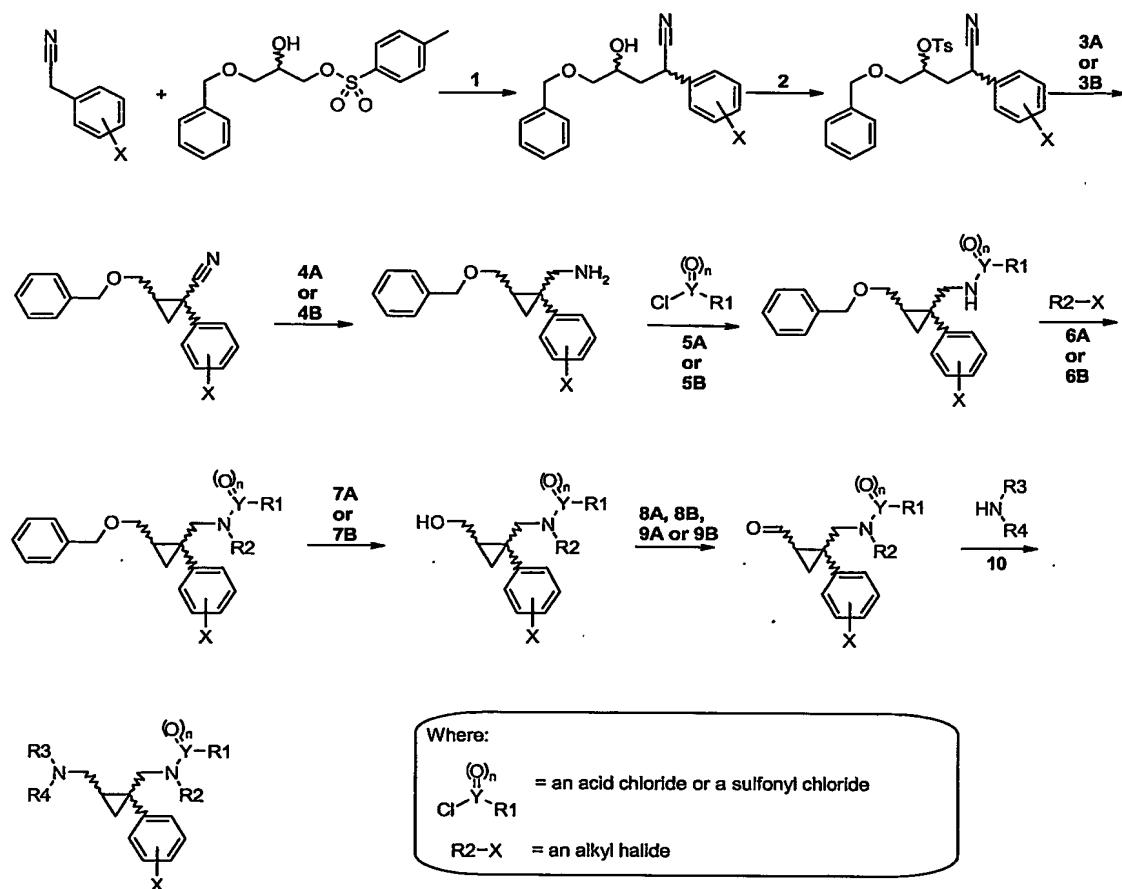
35

High Resolution Mass Spectra were acquired using Micromass LCT mass spectrometer (time-of-flight) with flow injection (FIA-MS) at 0.3 mL/min with 100% MeOH (0.1% formic acid), run time of 2 minutes, in ESI+ mode, scanning from 100-1100 amu @ 0.5 sec/scan. Reserpine was used as the lock mass (m/z 609.2812) and to adjust mass scale.

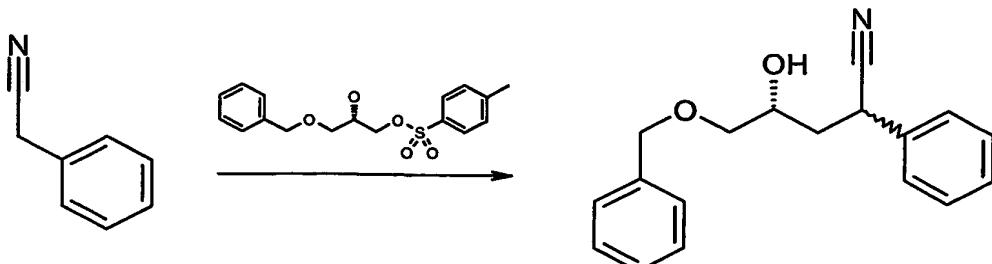
As will be appreciated by those skilled in the art, the following schemes may be followed in preparing the compounds of the present invention. The variability depicted within the scheme(s) illustrated herein, for example the variability of the "R" groups, should be limited to the particular scheme and not necessarily extended throughout the rest of the present specification.

5

Scheme 1:



Preparation 1: (4R)-4-hydroxy-2-phenyl-5-[(phenylmethyl)oxy]pentanenitrile

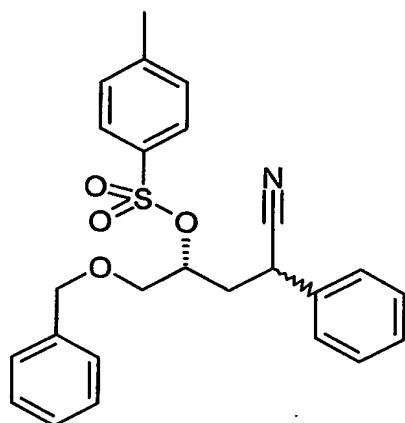


10

Phenylacetonitrile (4.59g, 39.2mmol) and (2S)-2-hydroxy-3-[(phenylmethyl)oxy]propyl 4-methylbenzenesulfonate (13.20g, 39.2mmol, 1eq) were dissolved in 50mL THF,

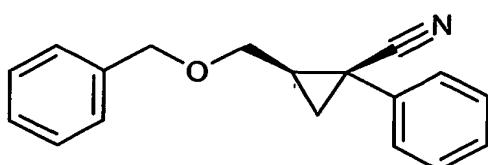
cooled to -78°C , and treated with 2.5M butyllithium in hexanes (35mL, 86.3mmol, 2.2eq) added dropwise over 30min. The reaction mixture was stirred 4h at -78°C , allowed to warm to ambient temperature and stirred an additional 16h. The reaction mixture was diluted with EtOAc, washed successively with water and brine, dried over MgSO_4 , filtered and concentrated to give the diastereomeric product as an orange oil in quantitative yield which was carried on without purification. ES-LCMS *m/z* 304.33 (M+Na).

Preparation 2: (1*R*)-3-cyano-3-phenyl-1-{{[(phenylmethyl)oxy]methyl}propyl 4-
10 methylbenzenesulfonate



(4*R*)-4-hydroxy-2-phenyl-5-[(phenylmethyl)oxy]pentanenitrile (16.0g, 57mmol), accessed via the method of preparation 1, was dissolved in 116mL CHCl_3 and 116mL Pyridine (25eq) with DMAP (0.70g, 5.7mmol, 0.1eq) and cooled to 0°C . 4-
15 methylbenzenesulfonyl chloride (43.5g, 228mmol, 4eq) was added to the reaction mixture and stirred 3 days at 0°C . The reaction mixture was washed successively with 1N HCl (4 x 250mL) and brine, dried over MgSO_4 , filtered and concentrated to a red oil. The crude material was purified by flash chromatography (SiO_2 , 10 \rightarrow 25% EtOAc/Hexanes) to give the diastereomeric product as a yellow oil (14.88g,
20 34.2mmol, 60%). ES-LCMS *m/z* 458.36 (M+Na).

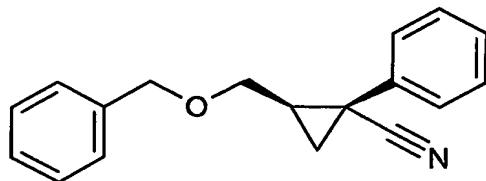
Preparation 3A: (1*S*,2*R*)-1-phenyl-2-
{{[(phenylmethyl)oxy]methyl}cyclopropanecarbonitrile



To (1*R*)-3-cyano-3-phenyl-1-{[(phenylmethyl)oxy]methyl}propyl 4-methylbenzenesulfonate (7.4g, 17.0mmol), accessed via the method of preparation 2, in 70mL DMF at -42°C was added 1M lithium bis(trimethylsilyl)amide in hexanes (25.5mL, 25.5mmol, 1.5eq) dropwise and stirred with continued cooling at -42°C for

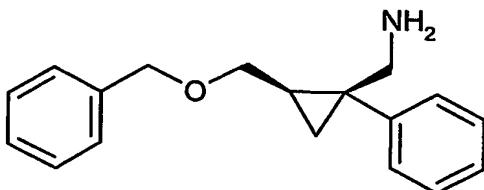
5 1h. The reaction mixture was diluted with EtOAc, washed successively with water (4x) and brine, dried over MgSO₄, filtered and concentrated to give the title compound (4.25g, 16.1mmol, 95%) as a yellow oil which was shown to be a 94:6 mix of the title compound to the product of Preparation 3B. ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.29 (m, 10H), 4.64 (m, 2H), 3.91-3.86 (m, 1H), 3.74-3.68 (m, 1H), 2.00-1.90 (m, 1H), 1.68-1.56 (m, 2H).

Preparation 3B: (1*R*,2*R*)-1-phenyl-2-[(phenylmethyl)oxy]methylcyclopropanecarbonitrile



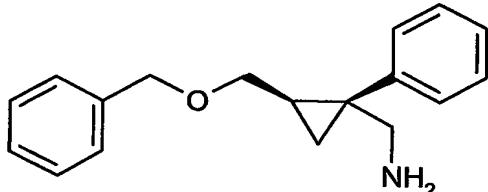
15 To 765mL toluene cooled to 0°C was added 1.0 M LHMDS in hexanes (148.1 mL, 148.1 mmol, 1 eq). To this solution was added (1*R*)-3-cyano-3-phenyl-1-[(phenylmethyl)oxy]methylpropyl 4-methylbenzenesulfonate (43.0 g, 98.73 mmol, 1eq), accessed via the method of Preparation 2, in 236mL toluene. The reaction mixture was stirred at 0°C for 16h, then washed successively with water and brine, dried over MgSO₄, filtered and concentrated to give a yellow oil that was shown to be an 8:2 diastereomeric mixture of the title compound to the product of Preparation 3A. The desired diastereomer (16.0 g, 62%) was separated by silica gel flash chromatography using 9:1 → 8:2 hexanes in ethyl acetate. ¹H NMR (300 MHz, CDCl₃) δ 7.44-7.15 (m, 10H), 4.28-4.19 (m, 2H), 3.31-3.27 (m, 1H), 2.94-2.84 (m, 1H), 2.22-2.15 (m, 1H), 1.76-1.72 (m, 1H), 1.47-1.44 (m, 1H). ES-LCMS *m/z* 264.1 (M+H).

Preparation 4A: [(1*S*,2*R*)-1-phenyl-2-[(phenylmethyl)oxy]methylcyclopropylmethyl]amine



To 16.2mL 1M lithium aluminum hydride(16.2mmol) in diethyl ether at 0°C (1S,2R)-1-phenyl-2-{{(phenylmethyl)oxy}methyl}cyclopropanecarbonitrile (4.25g, 16.2mmol), accessed via the method of Preparation 3A, dissolved in 17mL diethyl ether. After 5 complete addition, the reaction mixture was stirred at 0°C for 2h followed by 4h at ambient temperature. The reaction mixture was diluted with 360mL diethyl ether and quenched with successive addition of 0.6mL water, 0.6mL 15% NaOH, and 3.0mL water. The reaction mixture was filtered and the filtrate was concentrated to a clear oil. The oil was purified by flash chromatography (SiO₂, 3→5%CH₃OH/ EtOAc with 10 1%NH₄OH) to give the title product (3.08g, 11.5mmol, 71%) as a single diastereomer. ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.19 (m, 10H), 4.62-4.54 (m, 2H), 3.88 (m, 1H), 3.34 (m, 1H), 2.96 (d, *J* = 14.1Hz, 1H), 2.70 (d, *J* = 14.1Hz, 1H), 1.58 (m, 1H), 1.00 (m, 1H), 0.62 (m, 1H). ES-LCMS *m/z* 268.4 (M+H).

15 Preparation 4B: {{(1*R*,2*R*)-1-phenyl-2-
{(phenylmethyl)oxy}methyl}cyclopropyl}methyl]amine

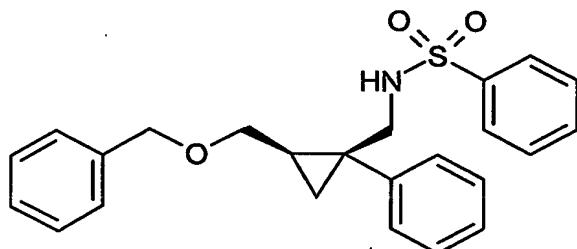


To 19.4mL 1M lithium aluminum hydride (19.4mmol) in diethyl ether at 0°C was 20 added (1*R*,2*R*)-1-phenyl-2-{{(phenylmethyl)oxy}methyl}cyclopropanecarbonitrile (5.10g, 19.4mmol), accessed via the method of Preparation 3B, dissolved in 20mL diethyl ether. After complete addition, the reaction mixture was stirred at 0°C for 3h. The reaction mixture was diluted with 360mL diethyl ether and quenched with successive addition of 0.6mL water, 0.6mL 15% NaOH, and 3.0mL water. The 25 reaction mixture was filtered and the filtrate was concentrated to a clear oil. The oil was purified by flash chromatography (SiO₂, 3→7%CH₃OH/ EtOAc with 1%NH₄OH) to give the title product (3.03g, 11.3mmol, 59%) as a single diastereomer. ¹H NMR (300 MHz, CDCl₃) δ 7.35-7.21 (m, 10H), 4.35-4.25 (m, 2H), 3.22-3.18 (m, 1H), 3.00-

2.94 (m, 2H), 2.43 (d, J = 13.5Hz, 1H), 1.36 (m, 1H), 0.91 (m, 1H), 0.78 (m, 1H). ES-LCMS m/z 268.4 (M+H).

Preparation 5A: *N*-[((1*S*,2*R*)-1-phenyl-2-

5 **{[(phenylmethyl)oxy]methyl}cyclopropyl)methyl]benzenesulfonamide**

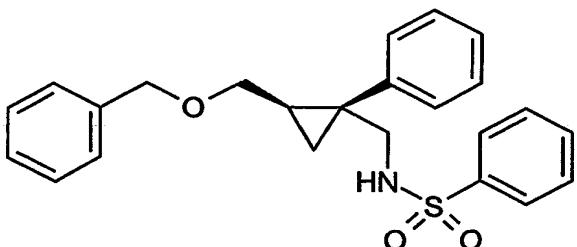


[((1*S*,2*R*)-1-phenyl-2-[(phenylmethyl)oxy]methyl]cyclopropyl)methyl]amine (1.00g, 3.74mmol), accessed via the method of Preparation 4A, was dissolved in 10mL DCE and combined with polymer-bound diisopropylamine (4.49mmol, 1.2eq).

10 Benzenesulfonyl chloride (1.06g, 5.98mmol, 1.6eq) was added and the reaction mixture agitated 16h at ambient temperature. Excess sulfonyl chloride was scavenged by addition of polymer-bound trisamine (4.49mmol, 1.2eq) with agitation at ambient temperature for 16h. The solid-supported reagents were filtered off,

15 washed successively with DCM, CH₃OH, THF, and DCM, the filtrates combined and concentrated to give the title product (1.52g, 100%) as an amber oil. ¹H NMR (300 MHz, CDCl₃) δ 8.04-8.02 (m, 1H), 7.75-7.15 (m, 14H), 5.67 (m, 1H), 4.55 (s, 2H), 3.90-3.86 (m, 1H), 3.57-3.51 (m, 1H), 3.12-3.07 (m, 1H), 2.90-2.85 (m, 1H), 1.62-1.56 (m, 1H), 1.03-0.99 (m, 1H), 0.66 (m, 1H). ES-LCMS m/z 430.1 (M+Na).

20 Preparation 5B: *N*-[((1*R*,2*R*)-1-phenyl-2-[(phenylmethyl)oxy]methyl]cyclopropyl)methyl]benzenesulfonamide



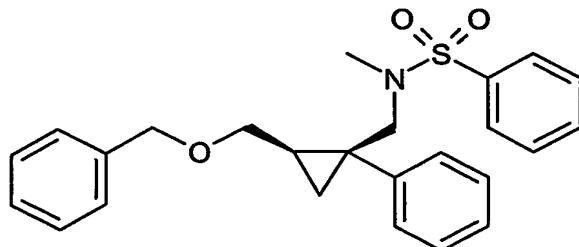
[((1*R*,2*R*)-1-phenyl-2-[(phenylmethyl)oxy]methyl]cyclopropyl)methyl]amine (1.00g, 3.74mmol), accessed via the method of preparation 4B, was dissolved in 10mL DCE

25 and combined with polymer-bound diisopropylamine (4.49mmol, 1.2eq).

Benzenesulfonyl chloride (1.06g, 5.98mmol, 1.6eq) was added and the reaction mixture agitated 16h at ambient temperature. Excess sulfonyl chloride was scavenged by addition of polymer-bound trisamine (4.49mmol, 1.2eq) with agitation at ambient temperature for 16h. The solid-supported reagents were filtered off,

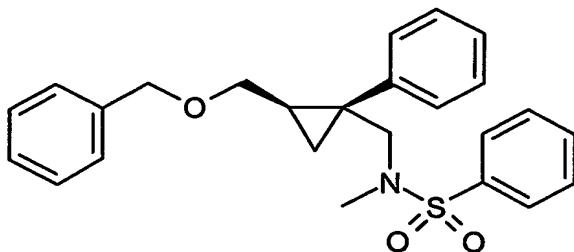
5 washed successively with DCM, CH₃OH, THF, and DCM, the filtrates combined and concentrated to give the title product (1.52g, 100%) as an amber oil. ¹H NMR (300 MHz, CDCl₃) δ 8.04-8.02 (m, 1H), 7.64-7.19 (m, 14H), 5.25 (m, 1H), 4.23 (ABq, J = 35.5, 11.4Hz, 2H), 3.28-3.24 (m, 1H), 3.15 (d, J = 12.7Hz, 1H), 2.90 (d, J = 12.7Hz, 1H), 2.82-2.77 (m, 1H), 1.36-1.31 (m, 1H), 0.96-0.92 (m, 1H), 0.76 (m, 1H). ES-
10 LCMS *m/z* 430.2 (M+Na).

Preparation 6A: *N*-methyl-*N*-[((1*S*,2*R*)-1-phenyl-2-
{[(phenylmethyl)oxy]methyl}cyclopropyl)methyl]benzenesulfonamide



15 Iodomethane (2.12g, 14.9mmol, 4eq) was added portionwise to *N*-[((1*S*,2*R*)-1-phenyl-2-
{[(phenylmethyl)oxy]methyl}cyclopropyl)methyl]benzenesulfonamide (1.71g, 3.74mmol, 1eq), accessed via the method of preparation 5A, in 7mL DMF with potassium carbonate (1.03g, 7.48mmol, 2eq) over 6h at 80°C. Following addition, the reaction mixture was stirred 16h at 80°C. The reaction mixture was diluted with
20 EtOAc, washed successively with saturated aqueous NaHCO₃, water (4x) and brine, dried over MgSO₄, filtered and concentrated to give a brown oil. The crude material was purified by flash chromatography (SiO₂, eluted successively with hexanes and EtOAc/hexanes (1:4)) to give the title product (1.57g, 100%) as a yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 7.58-7.19 (m, 15H), 4.57 (ABq, J = 24.3, 11.9Hz, 2H), 3.84-3.80 (m, 1H), 3.58-3.48 (m, 1H), 3.29 (d, J = 14.1Hz, 1H), 2.50 (s, 3H), 1.47 (m, 1H), 1.33 (m, 1H), 0.91 (m, 1H). ES-LCMS *m/z* 444.2 (M+Na).

Preparation 6B: *N*-methyl-*N*-[((1*R*,2*R*)-1-phenyl-2-
{[(phenylmethyl)oxy]methyl}cyclopropyl)methyl]benzenesulfonamide

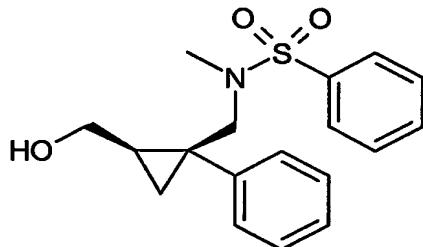


Iodomethane (2.12g, 14.9mmol, 4eq) was added portionwise to *N*-[((1*R*,2*R*)-1-phenyl-2-[(phenylmethyl)oxy]methyl)cyclopropyl)methyl]benzenesulfonamide (1.71g, 3.74mmol, 1eq), accessed via the method of preparation **5B**, in 7mL DMF with

5 potassium carbonate (1.03g, 7.48mmol, 2eq) over 6h at 80°C. Following addition, the reaction mixture was stirred 16h at 80°C. The reaction mixture was diluted with EtOAc, washed successively with saturated aqueous NaHCO₃, water (4x) and brine, dried over MgSO₄, filtered and concentrated to give a brown oil. The crude material was purified by flash chromatography (SiO₂, eluted successively with hexanes and

10 EtOAc/hexanes (1:4)) to give the title product (1.57g, 100%) as a yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 7.58-7.21 (m, 15H), 4.26 (ABq, *J* = 26.5, 11.7Hz, 2H), 3.50 (d, *J* = 14.0Hz, 1H), 3.23-3.20 (m, 1H), 2.94-2.89 (m, 2H), 2.54 (s, 3H), 1.39 (m, 1H), 1.10 (m, 1H), 0.92 (m, 1H). ES-LCMS *m/z* 444.3 (M+Na).

15 Preparation **7A**: *N*-[((1*S*,2*R*)-2-(hydroxymethyl)-1-phenylcyclopropyl)methyl]-*N*-methylbenzenesulfonamide

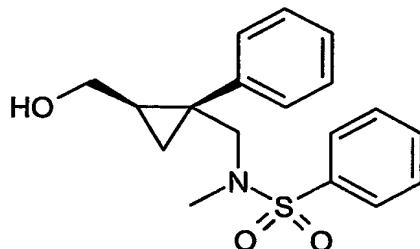


15 *N*-methyl-*N*-[((1*S*,2*R*)-1-phenyl-2-[(phenylmethyl)oxy]methyl)cyclopropyl)methyl]benzenesulfonamide (1.57g, 3.74mmol), accessed via the method of preparation **6A**, was combined with 10% palladium on activated carbon (0.35g) in EtOAc and hydrogenated under 1atm H₂(g) for 4h at ambient temperature. The catalyst was filtered off through celite and the filtrate concentrated to give the title product (1.17g, 3.53mmol, 95%) as a clear oil. ¹H NMR (300 MHz, CDCl₃) δ 7.68-7.18 (m, 10H), 4.07-4.03 (m, 1H), 3.72-3.66 (m, 1H),

3.55 (d, $J = 14.1$ Hz, 1H), 3.25 (d, $J = 14.1$ Hz, 1H), 2.36 (s, 3H), 1.59 (m, 1H), 1.18-1.15 (m, 1H), 0.79 (m, 1H). ES-LCMS m/z 354.3 (M+Na).

Preparation 7B: *N*-{[(1*R*,2*R*)-2-(hydroxymethyl)-1-phenylcyclopropyl]methyl}-*N*-

5 methylbenzenesulfonamide



N-methyl-*N*-{[(1*R*,2*R*)-1-phenyl-2-

6 {[(phenylmethyl)oxy]methyl}cyclopropyl)methyl]benzenesulfonamide (1.57g,

3.74mmol), accessed via the method of preparation 6B, was combined with 10%

10 palladium on activated carbon (0.35g) in EtOAc and hydrogenated under 1atm H₂(g) for 4h at ambient temperature. The catalyst was filtered off through celite and the

filtrate concentrated to give the title product (1.01g, 3.05mmol, 82%) as a clear oil. ¹H

NMR (300 MHz, CDCl₃) δ 7.63-7.61 (m, 2H), 7.53 (m, 1H), 7.46-7.43 (m, 2H), 7.33-

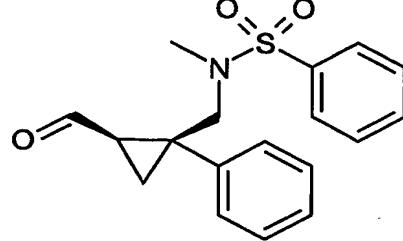
7.24 (m, 5H), 3.60 (d, $J = 13.8$ Hz, 1H), 3.40-3.35 (m, 1H), 3.20-3.14 (m, 1H), 2.92 (d,

15 $J = 13.8$ Hz, 1H), 2.55 (s, 3H), 1.43 (m, 1H), 1.10 (m, 1H), 0.99 (m, 1H). ES-LCMS

m/z 354.2 (M+Na).

Preparation 8A: *N*-{[(1*S*,2*R*)-2-formyl-1-phenylcyclopropyl]methyl}-*N*-

7 methylbenzenesulfonamide



20

N-{[(1*S*,2*R*)-2-(hydroxymethyl)-1-phenylcyclopropyl]methyl}-*N*-

21 methylbenzenesulfonamide (600mg, 1.82mmol), accessed via the method of

preparation 7A, was dissolved in 18mL DCM with 270uL 2-methylpropan-2-ol and

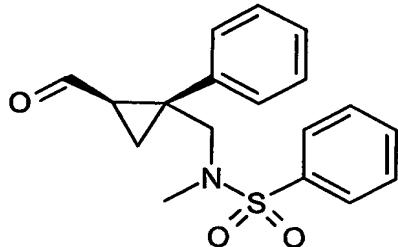
treated with Dess-Martin Periodinane (1.23g, 2.90mmol, 1.6eq) at ambient

25 temperature for 16h. The reaction mixture was diluted with 42mL diethyl ether and

treated with 22mL 1N NaOH at ambient temperature for 15min. The organic phase was separated, the aqueous phase extracted twice with diethyl ether, the organic phases combined, washed with brine, dried over MgSO₄, filtered and concentrated to a colorless oil. The crude material was purified by flash chromatography (SiO₂,

5 eluted successively with DCM, EtOAc/hexanes (1:4)) to the title product (270mg, 0.82mmol, 45%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 9.82 (d, J = 3.8Hz, 1H), 7.65-7.28 (m, 10H), 3.53-3.43 (m, 2H), 2.42 (s, 3H), 2.34-2.32 (m, 1H), 1.90-1.87 (m, 1H), 1.70-1.66 (m, 1H).

10 Preparation 8B: *N*-{[(1*R*,2*R*)-2-formyl-1-phenylcyclopropyl]methyl}-*N*-methylbenzenesulfonamide



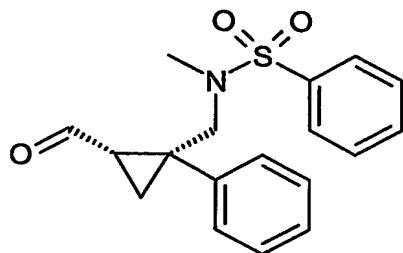
15 *N*-{[(1*R*,2*R*)-2-(hydroxymethyl)-1-phenylcyclopropyl]methyl}-*N*-methylbenzenesulfonamide (600mg, 1.82mmol), accessed via the method of preparation 7B, was dissolved in 18mL DCM with 270uL 2-methylpropan-2-ol and treated with Dess-Martin Periodinane (1.23g, 2.90mmol, 1.6eq) at ambient temperature for 16h. The reaction mixture was diluted with 42mL diethyl ether and treated with 22mL 1N NaOH at ambient temperature for 15min. The organic phase was separated, the aqueous phase extracted twice with diethyl ether, the organic phases combined, washed with brine, dried over MgSO₄, filtered and concentrated to a colorless oil. The crude material was purified by flash chromatography (SiO₂,

20 eluted successively with DCM, EtOAc/hexanes (1:4)) to the title product (410mg, 1.24mmol, 69%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 8.54 (d, J = 6.7Hz, 1H), 7.65 (m, 2H), 7.55 (m, 1H), 7.47 (m, 2H), 7.31-7.23 (m, 5H), 3.50 (d, J = 14.3Hz, 1H), 3.09 (d, J = 14.3Hz, 1H), 2.52 (s, 3H), 2.15-2.08 (m, 1H), 1.93 (m, 1H), 1.76-1.73 (m, 1H).

25

Preparation 9A: *N*-{[(1*R*,2*S*)-2-formyl-1-phenylcyclopropyl]methyl}-*N*-methylbenzenesulfonamide

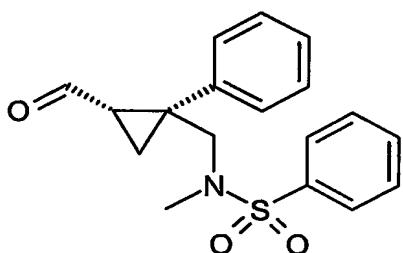
58



Starting from phenylacetonitrile and (2*R*)-2-hydroxy-3-[(phenylmethyl)oxy]propyl 4-methylbenzenesulfonate and using the methods of Preparations 1, 2, 3A, 4A, 5A, 6A, 7A, and 8A sequentially, the title product can be obtained in comparable yields

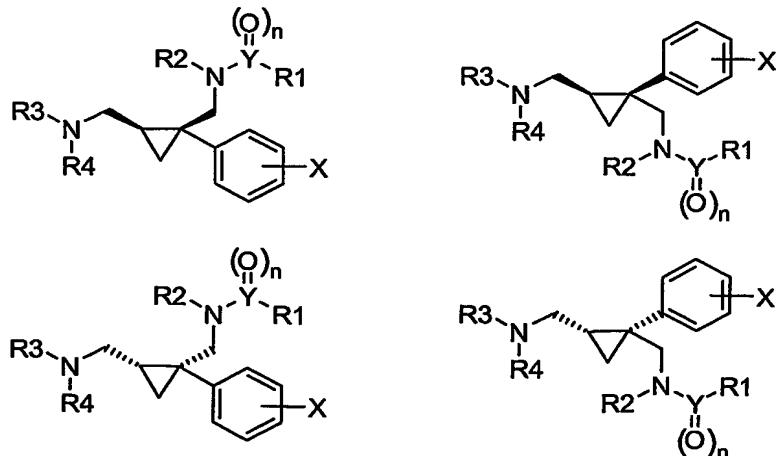
5 and analytical characterization to those obtained in those preparations.

Preparation 9B: *N*-{[(1*S*,2*S*)-2-formyl-1-phenylcyclopropyl]methyl}-*N*-methylbenzenesulfonamide



10 Starting from phenylacetonitrile and (2*R*)-2-hydroxy-3-[(phenylmethyl)oxy]propyl 4-methylbenzenesulfonate and using the methods of Preparations 1, 2, 3B, 4B, 5B, 6B, 7B, and 8B sequentially, the title product can be obtained in comparable yields and analytical characterization to those obtained in those preparations.

15 **Preparation 10: Compounds of general formula:**



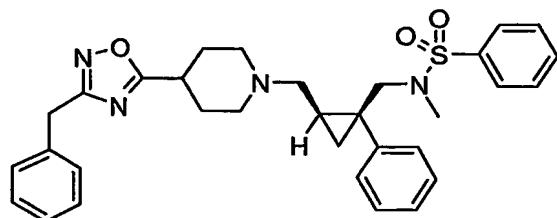
To aldehydes (33mg, 100 μ mol), made according to the methods of preparations **8A**, **8B**, **9A**, and **9B**, dissolved in 2mL DCE were added secondary amines (100 μ mol, 1eq) in 1mL DCM and treated with sodium triacetoxyborohydride (42mg, 200 μ mol, 2eq) at ambient temperature for 16h with continuous agitation. The

5 reaction mixtures were each treated with 4mL saturated aqueous NaHCO₃ with agitation for 1h, the organic phases separated via filtration through hydrophobic frit tube assemblies, and the organic filtrates concentrated to dryness. Crude products were dissolved in 300 microliters of DMSO and brought up to a final volume of 500 microliters using methanol. This 500 microliter solution was injected by a Waters
 10 2767 autosampler into an XTerra C18 5 micron particle HPLC column (19mmX150mm). Initial solvent flow was 20ml/min with 30% methanol and 70% water at a pH of 11 using ammonium hydroxide as buffer. Void volume was 2 minutes, and a linear gradient to 100% methanol in 10 minutes with a five minute wash at 100% methanol eluted the compound in approximately 10 minutes. A
 15 Micromass Platform LC mass spectrometer was used to monitor a split off the eluate for desired mass, and the purified fractions were collected using Micromass Fractionlynx software. Final products were obtained in moderate to good yields. Chiral HPLC was performed on representative samples to confirm that homochiral integrity had been preserved.

20

The following demonstrate the above-referenced general scheme:

Example 1: *N*-[((1*S*,2*R*)-2-{{[4-(3-benzyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl]methyl}-1-phenylcyclopropyl)methyl]-*N*-methylbenzenesulfonamide



25

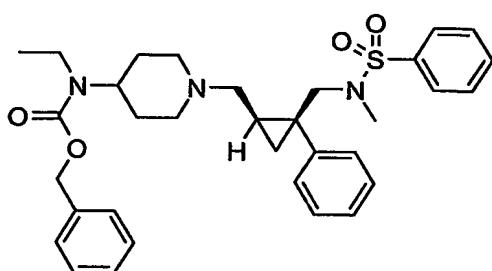
N-[(1*S*,2*R*)-2-formyl-1-phenylcyclopropyl]methyl]-*N*-methylbenzenesulfonamide and 4-(3-benzyl-1,2,4-oxadiazol-5-yl)piperidine (incorporating by reference as needed WO 00/39125) were reacted as per Preparation 10 to give the title compound.

¹H NMR (300 MHz, DMSO-d₆) δ 7.69-7.55 (m, 5H), 7.36-7.18 (m, 10H), 4.08 (s, 2H),
 30 3.91 (d, *J* = 13.2Hz, 1H), 3.08-2.98 (m, 2H), 2.81 (d, *J* = 13.2Hz, 1H), 2.84-2.78 (m,

1H), 2.59-2.43 (m, 2H), 2.52 (s, 3H), 2.27-1.97 (m, 4H), 1.80-1.66 (m, 2H), 1.45-1.39 (m, 1H), 1.09-0.99 (m, 1H), 0.80 (m, 1H). ES-LCMS *m/z* 557.2 (M+H).

Example 2: Benzyl ethyl{1-[((1*R*,2*S*)-2-{{[methyl(phenylsulfonyl)amino]methyl}-2-

5 phenylcyclopropyl)methyl]piperidin-4-yl}carbamate

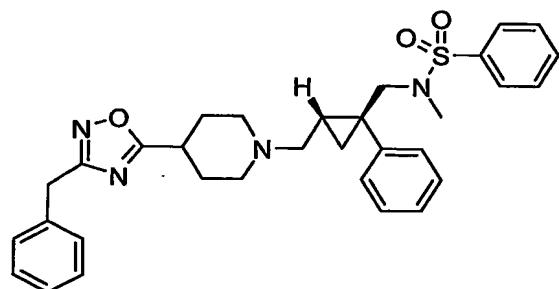


N-{[(1*S*,2*R*)-2-formyl-1-phenylcyclopropyl]methyl}-*N*-methylbenzenesulfonamide and benzyl ethyl(piperidin-4-yl)carbamate (incorporating by reference as needed *Bioorg. and Med. Chem. Lett.*, 11(2001), 2475) were reacted as per Preparation 10 to give

10 the title compound.

¹H NMR (300 MHz, DMSO-d₆) δ 7.70-7.56 (m, 5H), 7.40-7.17 (m, 10H), 5.09 (s, 2H), 3.88 (d, *J* = 13.3Hz, 1H), 3.75 (m, 1H), 3.19 (q, *J* = 6.6Hz, 2H), 3.09-3.05 (m, 1H), 2.91-2.87 (m, 1H), 2.83 (d, *J* = 13.3Hz, 1H), 2.58-2.52 (m, 1H), 2.52 (s, 3H), 2.44-2.38 (m, 1H), 2.08-1.92 (m, 2H), 1.77-1.58 (m, 4H), 1.41-1.37 (m, 1H), 1.07 (t, *J* = 6.6Hz, 3H), 1.07-0.99 (m, 1H), 0.78 (m, 1H). ES-LCMS *m/z* 576.1 (M+H).

Example 3: *N*-{[(1*S*,2*S*)-2-{{[4-(3-benzyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl]methyl}-1-phenylcyclopropyl)methyl]-*N*-methylbenzenesulfonamide

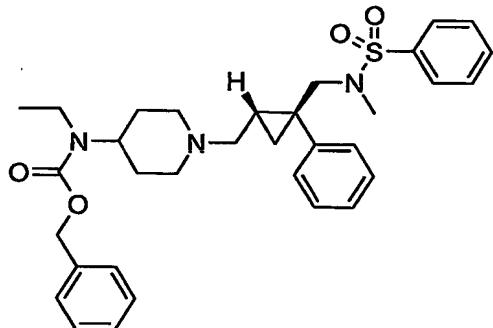


20 *N*-{[(1*S*,2*S*)-2-formyl-1-phenylcyclopropyl]methyl}-*N*-methylbenzenesulfonamide and 4-(3-benzyl-1,2,4-oxadiazol-5-yl)piperidine (incorporating by reference as needed WO 00/39125) were reacted as per Preparation 10 to give the title compound.

¹H NMR (300 MHz, DMSO-d₆) δ 7.69-7.54 (m, 5H), 7.35-7.20 (m, 10H), 4.06 (s, 2H), 3.55 (d, *J* = 13.8Hz, 1H), 2.97-2.85 (m, 1H), 2.78 (d, *J* = 13.8Hz, 1H), 2.64-2.59 (m,

1H), 2.53 (s, 3H), 2.27-2.21 (m, 1H), 2.02-1.88 (m, 4H), 1.75-1.61 (m, 2H), 1.48-1.41 (m, 1H), 1.17 (m, 1H), 1.07-1.02 (m, 1H), 0.93-0.89 (m, 1H). ES-LCMS *m/z* 557.1 (M+H).

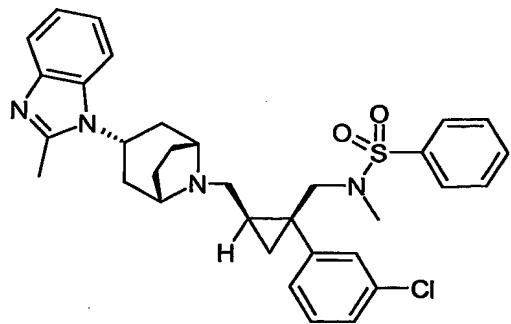
5 Example 4: *benzyl ethyl{1-[(1S,2S)-2-[(methyl(phenylsulfonyl)amino)methyl]-2-phenylcyclopropyl)methyl}piperidin-4-yl}carbamate*



N-[(1S,2S)-2-formyl-1-phenylcyclopropyl)methyl]-N-methylbenzenesulfonamide and benzyl ethyl(piperidin-4-yl)carbamate (incorporating by reference as needed *Bioorg. and Med. Chem. Lett.*, 11(2001), 2475) were reacted as per Preparation 10 to give the title compound.

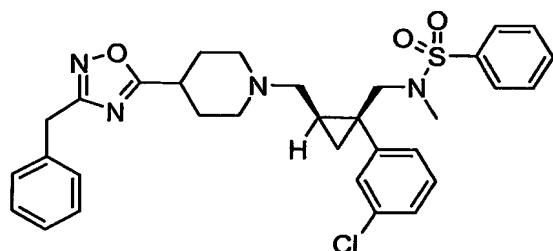
10 ¹H NMR (300 MHz, DMSO-d₆) δ 7.67-7.55 (m, 5H), 7.39-7.21 (m, 10H), 5.07 (s, 2H), 3.67 (m, 1H), 3.57 (d, *J* = 13.3 Hz, 1H), 3.17 (q, *J* = 6.6 Hz, 2H), 2.99-2.93 (m, 1H), 2.76 (d, *J* = 13.3 Hz, 1H), 2.75-2.68 (m, 1H), 2.52 (s, 3H), 2.29-2.19 (m, 1H), 1.87-1.38 (m, 7H), 1.11 (m, 1H), 1.04 (t, *J* = 6.6 Hz, 3H), 1.07-1.03 (m, 1H), 0.90 (m, 1H). ES-LCMS *m/z* 576.2 (M+H).

15 Example 5: *N-[(1S,2R)-1-(3-chlorophenyl)-2-[(3-exo)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl)methyl]cyclopropyl)methyl]-N-methylbenzenesulfonamide*



N-{[(1*S*,2*R*)-1-(3-chlorophenyl)-2-formylcyclopropyl]methyl}-*N*-methylbenzenesulfonamide [made from (3-chlorophenyl)acetonitrile via the sequential methods of Preparations 1, 2, 3A, 4A, 5A, 6A, 7A, 8A] and 1-[(3-exo)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole (incorporating by reference as needed WO 00/38680) were reacted as per Preparation 10 to give the title compound. ES-LCMS *m/z* 589.6 (M+H).

Example 6: *N*-{[(1*S*,2*R*)-2-[(4-(3-benzyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)methyl]-1-(3-chlorophenyl)cyclopropyl]methyl}-*N*-methylbenzenesulfonamide

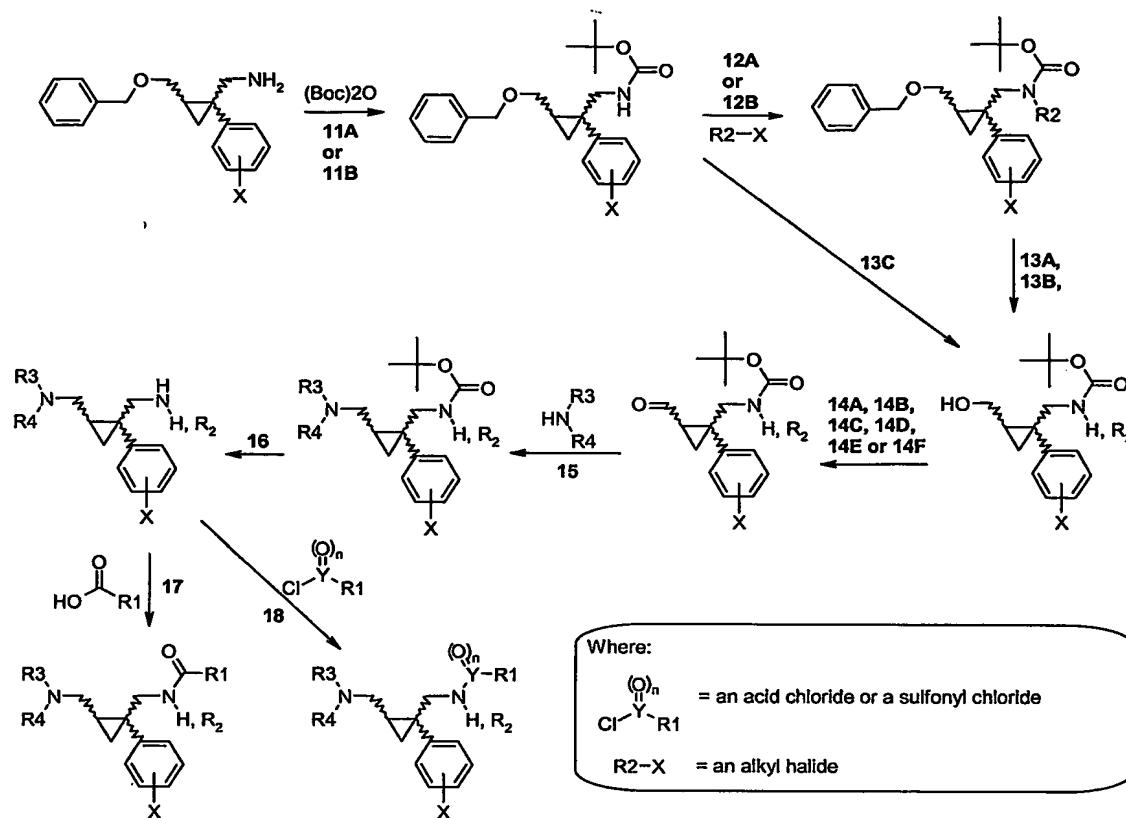


10

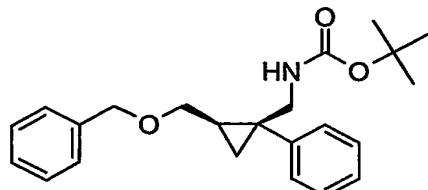
N-{[(1*S*,2*R*)-1-(3-chlorophenyl)-2-formylcyclopropyl]methyl}-*N*-methylbenzenesulfonamide [made from (3-chlorophenyl)acetonitrile via the sequential methods of Preparations 1, 2, 3A, 4A, 5A, 6A, 7A, 8A] and 4-(3-benzyl-1,2,4-oxadiazol-5-yl)piperidine (incorporating by reference as needed WO 00/39125) were reacted as per Preparation 10 to give the title compound.

¹H NMR (300 MHz, CD₃OD) δ 7.70-7.53 (m, 5H), 7.36-7.23 (m, 9H), 4.07 (s, 2H), 3.83 (d, *J* = 14.0Hz, 1H), 3.39-3.16 (m, 4H), 3.09 (d, *J* = 14.0Hz, 1H), 2.78-2.61 (m, 3H), 2.57 (s, 3H), 2.28-2.21 (m, 2H), 2.07-1.94 (m, 2H), 1.53-1.48 (m, 1H), 1.33-1.29 (m, 1H), 1.00-0.96 (m, 1H). ES-LCMS *m/z* 591.5 (M+H).

Scheme 2:



Preparation 11A: 1,1-dimethylethyl [((1*S*,2*R*)-1-phenyl-2-
 {[(phenylmethyl)oxy]methyl}cyclopropyl)methyl]carbamate



5

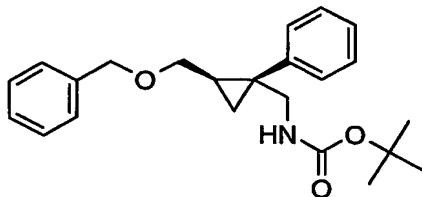
To a solution of [((1*S*,2*R*)-1-phenyl-2-
 {[(phenylmethyl)oxy]methyl}cyclopropyl)methyl]amine (28.53g, 107mmol, 1eq),
 accessed via the method of preparation 4A, and triethylamine (11.9g, 117mmol,
 1.1eq) in 380mL DCM cooled to 0°C was added di(*tert*-butyl) dicarbonate (24.45g,

10 112mmol, 1.05eq). The resultant mixture was stirred 2h at 0°C followed by 16h at
 ambient temperature. The reaction mixture was diluted with DCM, washed
 successively with saturated NaHCO₃ and brine, dried over MgSO₄, filtered and
 concentrated to give the title compound (39.3g, 107mmol, 100%) as an amber oil. ¹H
 NMR (300 MHz, CDCl₃) δ 7.43-7.17(m, 10H), 5.35 (d, J=7.8Hz, 1H), 4.60 (m, 2H),

3.95 (m, 2H), 3.35 (t, $J=10.3$ Hz, 1H), 2.97 (dd, $J=13.9, 2.1$ Hz, 1H), 1.62 (m, 1H), 1.35 (s, 9H), 1.08 (m, 1H), 0.77 (t, $J=5.4$ Hz, 1H). ES-LCMS m/z 390.30 (M+Na).

Preparation 11B: 1,1-dimethylethyl [($1R,2R$)-1-phenyl-2-

5 {[(phenylmethyl)oxy]methyl}cyclopropyl)methyl]carbamate



To a solution of [($1R,2R$)-1-phenyl-2-

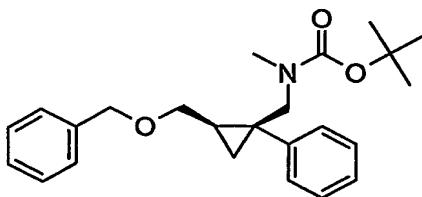
{[(phenylmethyl)oxy]methyl}cyclopropyl)methyl]amine (12.6g, 47.13mmol, 1eq),

accessed via the method of **4B**, and triethylamine (5.25g, 51.8mmol, 1.1eq) in 200mL

10 DCM cooled to 0°C was added di(*tert*-butyl) dicarbonate (10.79g, 49.48mmol, 1.05eq). The resultant mixture was stirred 2h at 0°C followed by 16h at ambient temperature. The reaction mixture was diluted with DCM, washed successively with saturated NaHCO₃ and brine, dried over MgSO₄, filtered and concentrated to give the title compound (16.6g, 45.17mmol, 96%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.42-7.14 (m, 10H), 4.50 (m, 1H), 4.35-4.25 (m, 2H), 3.50-3.45 (m, 1H), 3.21-3.17 (m, 1H), 3.10-3.05 (m, 1H), 3.00-2.95 (m, 1H), 1.36 (s, 9H), 1.07-1.04 (m, 1H), 0.82-0.798(m, 1H). ES-LCMS m/z 368.2 (M+H).

Preparation 12A: 1,1-dimethylethyl methyl[[($1S,2R$)-1-phenyl-2-

20 {[(phenylmethyl)oxy]methyl}cyclopropyl)methyl]carbamate



To a solution of 1,1-dimethylethyl [($1S,2R$)-1-phenyl-2-

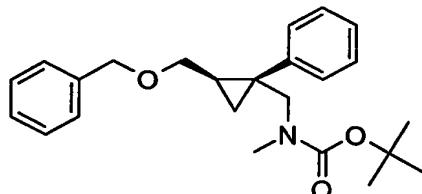
{[(phenylmethyl)oxy]methyl}cyclopropyl)methyl]carbamate (39.2g, 92mmol),

accessed via the method of **11A**, and methyl iodide (39.2g, 276mmol, 3eq) in 300mL

25 THF cooled to 0°C was added 1M sodium bis(trimethylsilyl)amide in THF (138mL, 138mmol, 1.5eq). The reaction mixture was stirred 2h at 0°C followed by 16h at ambient temperature. The reaction mixture was partitioned between EtOAc and water, the phases separated, the aqueous phase extracted twice with EtOAc, the

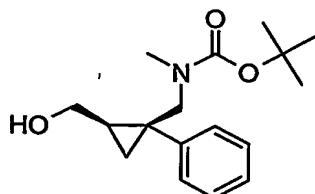
organic phases combined, washed with brine, dried over MgSO_4 , filtered and concentrated to an amber oil. The crude material was purified by flash chromatography (SiO_2 , eluted successively with $\text{DCM}/\text{hexanes}$ (1:1), DCM , and $\text{EtOAc}/\text{hexanes}$ (1:4)) to give the title compound (22.25g, 58mmol, 63%) as a pale yellow oil. ES-LCMS m/z 404.30($\text{M}+\text{Na}$).

Preparation 12B: 1,1-dimethylethyl methyl[[(1*R*,2*R*)-1-phenyl-2-[(phenylmethyl)oxy]methyl]cyclopropyl]methyl]carbamate



10 To a solution of 1,1-dimethylethyl [[(1*R*,2*R*)-1-phenyl-2-[(phenylmethyl)oxy]methyl]cyclopropyl]methyl]carbamate (7.5g, 20.4mmol), accessed via the method of 11B, and methyl iodide (14.4g, 102.0mmol, 5eq) in 100mL THF cooled to 0°C was added 1M sodium bis(trimethylsilyl)amide in THF (30.6mL, 30.6mmol, 1.5eq). The reaction mixture was stirred 8h at 0°C followed by 15 16h at ambient temperature. The reaction mixture was partitioned between EtOAc and water, the phases separated, the aqueous phase extracted twice with EtOAc , the organic phases combined, washed with brine, dried over MgSO_4 , filtered and concentrated to an amber oil. The crude material was purified by flash chromatography (SiO_2 , eluted with $\text{EtOAc}/\text{hexanes}$ (1:4)) to give the title compound (20 23.1g, 8.1mmol, 40%) as a pale yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.34-7.18 (m, 10H), 4.36-4.27 (m, 2H), 3.67-3.45 (m, 1H), 3.26-3.13 (m, 2H), 3.07-2.99 (m, 1H), 2.77-2.62 (m, 3H), 1.39-0.80 (m, 12H). ES-LCMS m/z 404.2 ($\text{M}+\text{Na}$).

Preparation 13A: 1,1-dimethylethyl [(1*S*,2*R*)-2-(hydroxymethyl)-1-phenylcyclopropyl]methyl]methylcarbamate

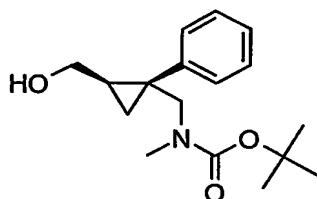


1,1-dimethylethyl methyl[[(1*S*,2*R*)-1-phenyl-2-[(phenylmethyl)oxy]methyl]cyclopropyl]methyl]carbamate (20.65g, 54mmol),

accessed via the method of Preparation 12A, was combined with 10% palladium on activated carbon (2.00g) in 250mL ethyl alcohol and hydrogenated under 1atm H₂(g) for 3h at ambient temperature. The catalyst was filtered off through celite and the filtrate concentrated to a yellow oil. The crude material was purified by flash

5 chromatography on silica eluted with 5→25%EtOAc/DCM. Appropriate fractions were combined and concentrated to give the title compound (12.02g, 41.2mmol, 76%) as a colorless oil. ¹H NMR (300 MHz, DMSO-d6, 90°C) δ 7.30-7.22 (m, 9H), 7.15 (m, 1H), 4.41 (t, J=5.1Hz, 1H), 3.87 (d, J=14.5Hz, 1H), 3.74 (m, 1H), 3.52 (m, 1H), 3.31 (d, J=14.4Hz, 1H), 2.63 (s, 3H), 1.21 (s, 9H), 1.20-1.07 (m, 2H), 0.77 (m, 1H). ES-LCMS *m/z* 314.21 (M+Na).

10 Preparation 13B: 1,1-dimethylethyl {[[(1*R*,2*R*)-2-(hydroxymethyl)-1-phenylcyclopropyl]methyl}methylcarbamate

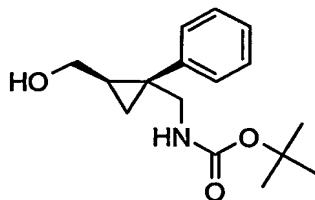


15 1,1-dimethylethyl methyl{[(1*R*,2*R*)-1-phenyl-2-
{[(phenylmethyl)oxy]methyl}cyclopropyl)methyl]carbamate (3.1g, 8.1mmol), accessed
via the method of Preparation 12B, was combined with 10% palladium on activated
carbon (0.50g) in ethyl alcohol and hydrogenated under 1atm H₂(g) for 0.5h at
ambient temperature. The catalyst was filtered off through celite and the filtrate
20 concentrated to a colorless oil. The crude material was purified by flash
chromatography (SiO₂, eluted with EtOAc/hexanes (4:6)) to give the title compound
(2.2g, 7.5mmol, 95%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.32-7.20 (m,
5H), 3.70-3.54 (m, 1H), 3.34-3.18 (m, 3H), 2.76-2.60 (m, 3H), 1.41-1.22 (m, 11H),
1.00 (m, 1H), 0.87-0.85 (m, 1H). ES-LCMS *m/z* 314.1 (M+Na).

25

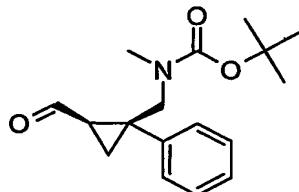
Preparation 13C: 1,1-dimethylethyl {[[(1*R*,2*R*)-2-(hydroxymethyl)-1-
phenylcyclopropyl]methyl}carbamate

67



1,1-dimethylethyl [((1R,2R)-1-phenyl-2-((phenylmethyl)oxy)methyl)cyclopropyl]carbamate (8.0g, 21.7mmol), accessed via the method of Preparation 11B, was combined with 10% palladium on activated carbon (0.8g) in ethyl alcohol and hydrogenated under 1atm H₂(g) for 2.5h at ambient temperature. The catalyst was filtered off through celite and the filtrate concentrated to a colorless oil. The crude material was purified by flash chromatography (SiO₂, eluted with EtOAc/hexanes (4:6)) to give the title compound (5.8g, 20.9mmol, 96%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.25 (m, 5H), 3.52-3.48 (m, 1H), 3.35-3.30 (m, 1H), 3.23-3.19 (m, 1H), 3.10-3.07 (m, 1H), 1.45-1.37 (m, 1H), 1.04-1.04 (m, 1H), 0.87-0.84 (m, 1H). LCMS *m/z* 300.1 (M+Na).

Preparation 14A: 1,1-dimethylethyl {[(1S,2R)-2-formyl-1-phenylcyclopropyl]methyl}methylcarbamate

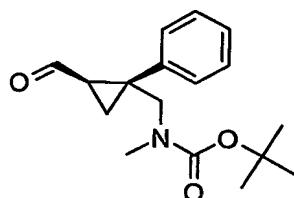


1,1-dimethylethyl {[(1S,2R)-2-(hydroxymethyl)-1-phenylcyclopropyl]methyl}methylcarbamate (12.02g, 41.2mmol), accessed via the method of Preparation 13A, was dissolved in 200mL DCM with 6.2mL 2-methylpropan-2-ol and treated with Dess-Martin Periodinane (28.0g, 66.0mmol, 1.6eq) in 200mL DCM at ambient temperature for 3h. The reaction mixture was diluted with 1L diethyl ether and treated with 400mL 1N NaOH at ambient temperature for 30min. The organic phase was separated, the aqueous phase extracted twice with diethyl ether, the organic phases combined, washed with brine, dried over MgSO₄, filtered and concentrated to a colorless oil. The crude material was purified by flash chromatography (SiO₂, eluted with EtOAc/hexanes (1:4)) to give the title compound (10.7, 36.9mmol, 89%). ¹H NMR (400 MHz, CDCl₃) δ 9.77-9.65

(m, 1H), 7.33-7.23 (m, 5H), 3.75-3.63 (m, 2H), 2.72-2.50 (m, 3H), 2.26-2.19 (m, 1H), 1.87-1.81 (m, 1H), 1.65-1.61 (m, 1H), 1.31-1.18 (m, 9H). LCMS *m/z* 312.2 (M+Na).

Preparation 14B: 1,1-dimethylethyl {[*(1R,2R)*-2-formyl-1-

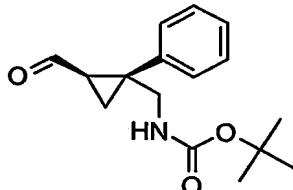
5 phenylcyclopropyl]methyl}methylcarbamate



1,1-dimethylethyl {[*(1R,2R)*-2-(hydroxymethyl)-1-phenylcyclopropyl]methyl}methylcarbamate (3.8g, 13.0mmol), accessed via the method of Preparation 13B, was dissolved in 35mL DCM with 1.1mL 2-methylpropan-2-ol and treated with Dess-Martin Periodinane (8.8g, 20.8mmol, 1.6eq) in 35mL DCM at ambient temperature for 2h. The reaction mixture was diluted with 50mL diethyl ether and treated with 50mL 1N NaOH at ambient temperature for 15min. The organic phase was separated, the aqueous phase extracted twice with diethyl ether, the organic phases combined, washed with brine, dried over MgSO₄, filtered and concentrated to a colorless oil. The crude material was purified by flash chromatography (SiO₂, eluted EtOAc/hexanes (3:7)) to give the title compound (3.2g, 11.0mmol, 84%). ¹H NMR (400 MHz, CDCl₃) δ 8.49-8.47 (m, 1H), 7.29-7.24 (m, 5H), 3.62-3.58 (m, 1H), 3.33-3.22 (m, 1H), 2.72-2.58 (m, 3H), 1.84-1.81 (m, 1H), 1.71-1.53 (m, 1H), 1.34-1.25 (m, 10H). ES-LCMS *m/z* 312.2 (M+Na).

20

Preparation 14C: 1,1-dimethylethyl {[*(1R,2R)*-2-formyl-1-phenylcyclopropyl]methyl}carbamate



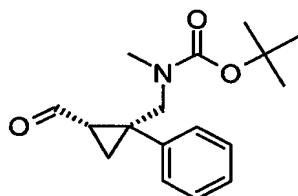
1,1-dimethylethyl {[*(1R,2R)*-2-(hydroxymethyl)-1-phenylcyclopropyl]methyl}carbamate (5.8g, 20.9mmol), accessed via the method of Preparation 13C, was dissolved in 100mL DCM with 3.1mL 2-methylpropan-2-ol and treated with Dess-Martin Periodinane (14.1g, 33.4mmol, 1.6eq) in 100mL DCM at ambient temperature for 3h. The reaction mixture was diluted with 500mL diethyl ether and treated with 200mL

1N NaOH at ambient temperature for 15min. The organic phase was separated, the aqueous phase extracted twice with diethyl ether, the organic phases combined, washed with brine, dried over MgSO₄, filtered and concentrated to a colorless oil.

The crude material was purified by flash chromatography (SiO₂, eluted with

5 EtOAc/hexanes (1:4)) to give the title compound (4.2g, 15.2mmol, 73%). ¹H NMR (400 MHz, CDCl₃) δ 8.51-8.50 (m, 1H), 7.34-7.24 (m, 5H), 4.55 (m, 1H), 3.44-3.39 (m, 1H), 3.25-3.20 (m, 1H), 2.13-2.08 (m, 1H), 1.80-1.78 (m, 1H), 1.64-1.61 (m, 1H), 1.37 (s, 9H). ES-LCMS *m/z* 298.1 (M+Na).

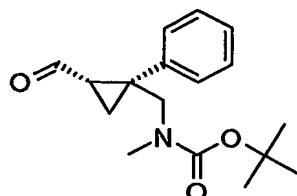
10 Preparation 14D: 1,1-dimethylethyl {[*(1R,2S)*-2-formyl-1-phenylcyclopropyl]methyl}methylcarbamate



Starting from phenylacetonitrile and (2*R*)-2-hydroxy-3-[(phenylmethyl)oxy]propyl 4-methylbenzenesulfonate and using the methods of Preparations 1, 2, 3A, 4A, 11A,

15 12A, 13A and 14A sequentially, the title product can be obtained in comparable yields and analytical characterization to those obtained in those preparations.

Preparation 14E: 1,1-dimethylethyl {[*(1S,2S)*-2-formyl-1-phenylcyclopropyl]methyl}methylcarbamate

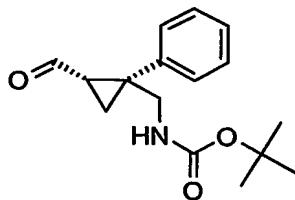


20

Starting from phenylacetonitrile and (2*R*)-2-hydroxy-3-[(phenylmethyl)oxy]propyl 4-methylbenzenesulfonate and using the methods of Preparations 1, 2, 3B, 4B, 11B, 12B, 13B, and 14B sequentially, the title product can be obtained in comparable yields and analytical characterization to those obtained in those preparations.

25

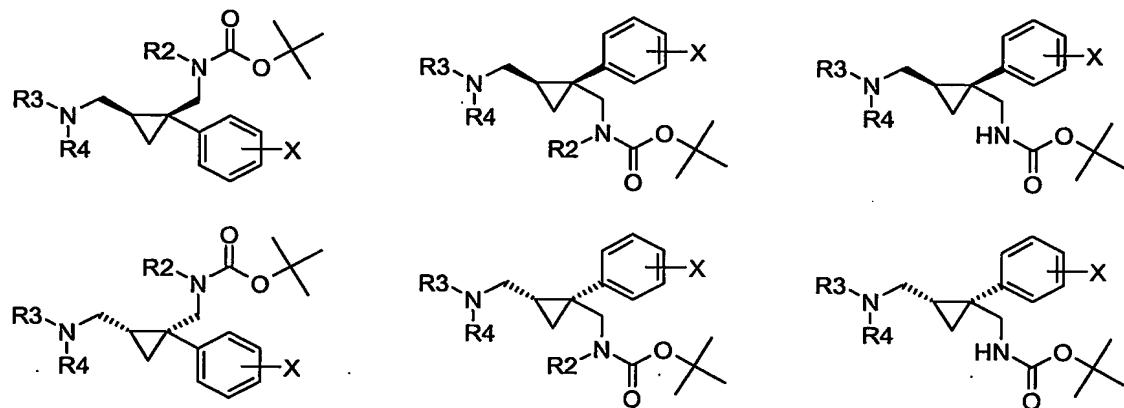
Preparation 14F: 1,1-dimethylethyl {[*(1S,2S)*-2-formyl-1-phenylcyclopropyl]methyl}carbamate



Starting from phenylacetonitrile and (2*R*)-2-hydroxy-3-[(phenylmethyl)oxy]propyl 4-methylbenzenesulfonate and using the methods of **Preparations 1, 2, 3B, 4B, 11B, 13C, and 14C** sequentially, the title product can be obtained in comparable yields

5 and analytical characterization to those obtained in those preparations.

Preparation 15: Compounds of generic structure:

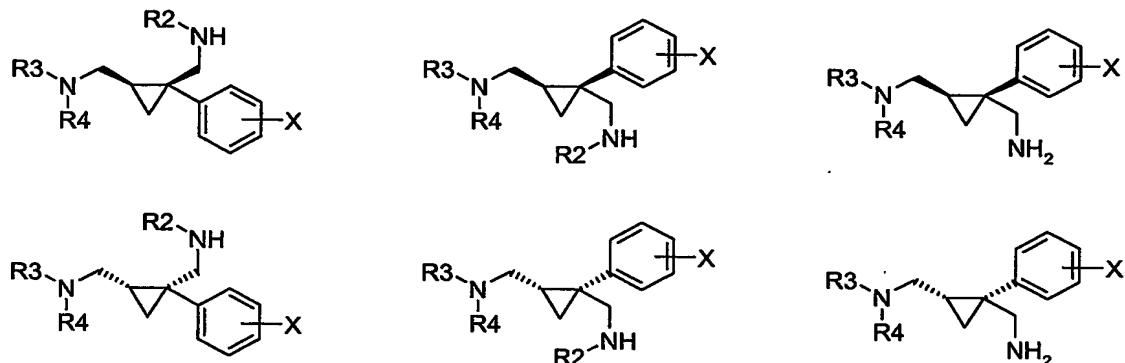


In combinatorial fashion, aldehydes prepared by the methods of **Preparations 14A-F**

10 (0.35mmol) in 3mL DCE were treated with various secondary amines (0.35mmol, 1eq) and mp-sodium triacetoxyborohydride (500mg, 1.04mmol, 3eq) at ambient temperature for 20h with continuous agitation. The reaction mixtures were each filtered. The remaining resin was treated with 4mL DCM with agitation for 1h and the organics separated via filtration. The organic filtrates were concentrated to dryness

15 and carried forward without purification or characterization.

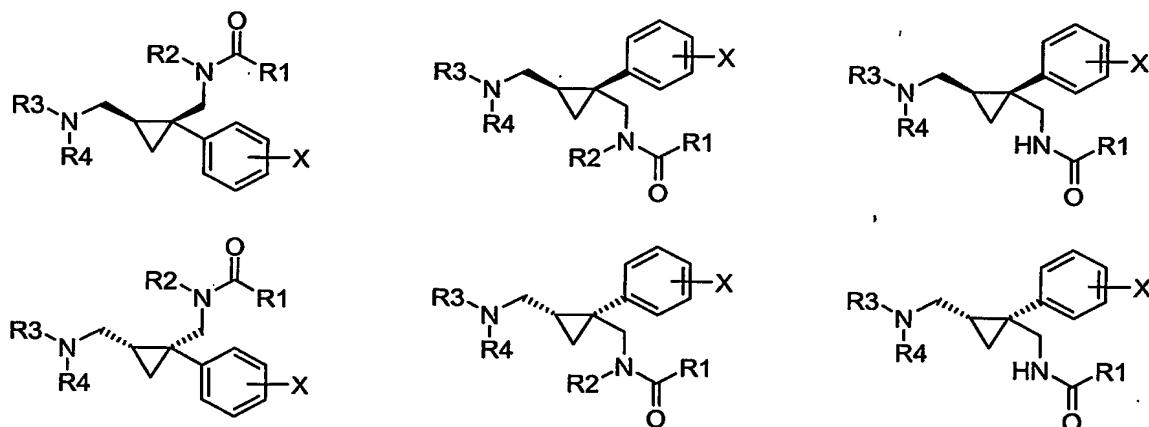
Preparation 16: Compounds of generic structure:



Compounds prepared by the method of Preparation 15 were treated with 1mL trifluoroacetic acid in 2mL DCM and 2mL DCE for 5h at ambient temperature with

5 slight agitation. The reaction mixtures were concentrated and partitioned between DCM (2mL) and saturated NaHCO₃ (2mL) and the organic phases separated via filtration through hydrophobic frit tube assemblies. The organic filtrates were concentrated to dryness and carried forward without purification or characterization.

10 Preparation 17: Compounds of general formula:



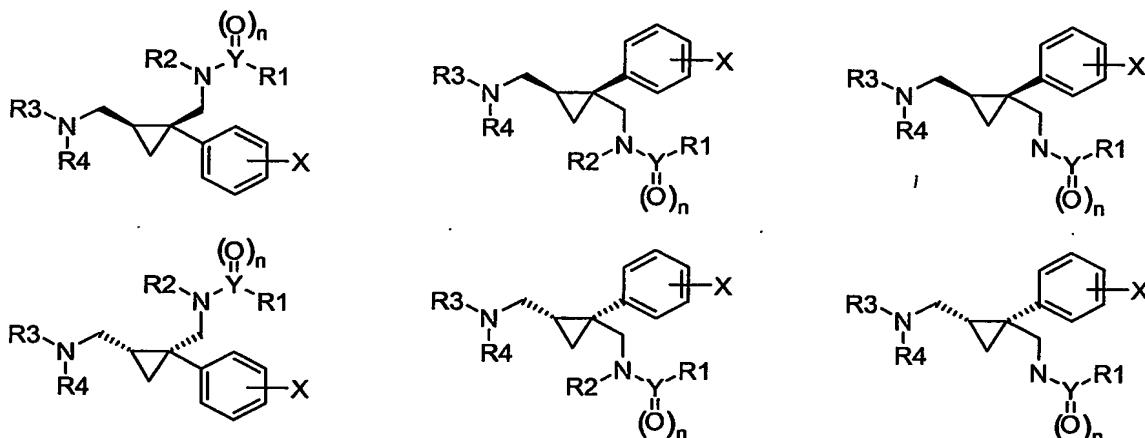
The compounds prepared according to the method of Preparation 16 were dissolved in 3mL DCE and further split out in combinatorial fashion such that each reaction was

15 performed on a theoretical scale of 0.12mmol in 1mL DCE. The reaction plates were concentrated down and the residues taken up in 1mL DMF for reaction. Polymer-bound diisopropylamine (0.48mmol, 4eq) was added to each well followed by an acid (0.13mmol, 1.1eq) in 0.5mL DMF and HATU (0.12mmol, 1eq) in 0.5 mL DMF. The resultant reaction mixtures were agitated at ambient temperature for 18h and HATU 20 byproducts scavenged by addition of polymer-bound carbonate (0.36mmol, 3eq) and

agitation at ambient temperature for 3h. The reaction plates were filtered and the filtrates concentrated to dryness. Crude products were dissolved in 300 microliters of DMSO and brought up to a final volume of 500 microliters using methanol. This 500 microliter solution was injected by a Waters 2767 autosampler into an XTerra C18 5

5 micron particle HPLC column (19mmX150mm). Initial solvent flow was 20ml/min with 30% methanol and 70% water at a pH of 11 using ammonium hydroxide as buffer. Void volume was 2 minutes, and a linear gradient to 100% methanol in 10 minutes with a five minute wash at 100% methanol eluted the compound in approximately 10 minutes. A Micromass Platform LC mass spectrometer was used
 10 to monitor a split off the eluate for desired mass, and the purified fractions were collected using Micromass Fractionlynx software. Chiral HPLC was performed on representative samples to confirm that homochiral integrity had been preserved.

Preparation 18: Compounds of general formula:



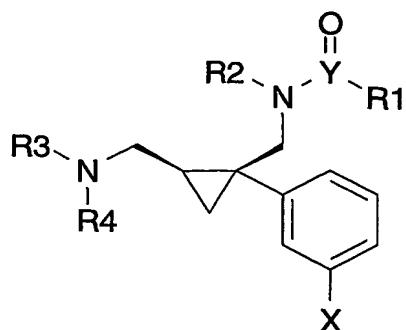
15

The compounds prepared according to the method of Preparation 16 were dissolved in 3mL DCE (1:1) and further split out in combinatorial fashion such that each reaction was performed on a theoretical scale of 0.12mmol in 1mL DCE. Polymer-bound diisopropylamine (0.48mmol, 4eq) was added to each well followed by either an acid chloride or sulfonyl chloride (0.12mol, 1eq) in 1mL DCE. The resultant reaction mixtures were agitated at ambient temperature for 16h and excess acid or sulfonyl chloride scavenged by addition of polymer-bound trisamine (0.36mmol, 3eq) and agitation at ambient temperature for 4h. The reaction plates were filtered and the filtrates concentrated to dryness. Crude products were dissolved in 300 microliters of DMSO and brought up to a final volume of 500 microliters using methanol. This 500 microliter solution was injected by a Waters 2767 autosampler

into an XTerra C18 5 micron particle HPLC column (19mmX150mm). Initial solvent flow was 20ml/min with 30% methanol and 70% water at a pH of 11 using ammonium hydroxide as buffer. Void volume was 2 minutes, and a linear gradient to 100% methanol in 10 minutes with a five minute wash at 100% methanol eluted the compound in approximately 10 minutes. A Micromass Platform LC mass spectrometer was used to monitor a split off the eluate for desired mass, and the purified fractions were collected using Micromass Fractionlynx software. Chiral HPLC was performed on representative samples to confirm that homochiral integrity had been preserved.

10

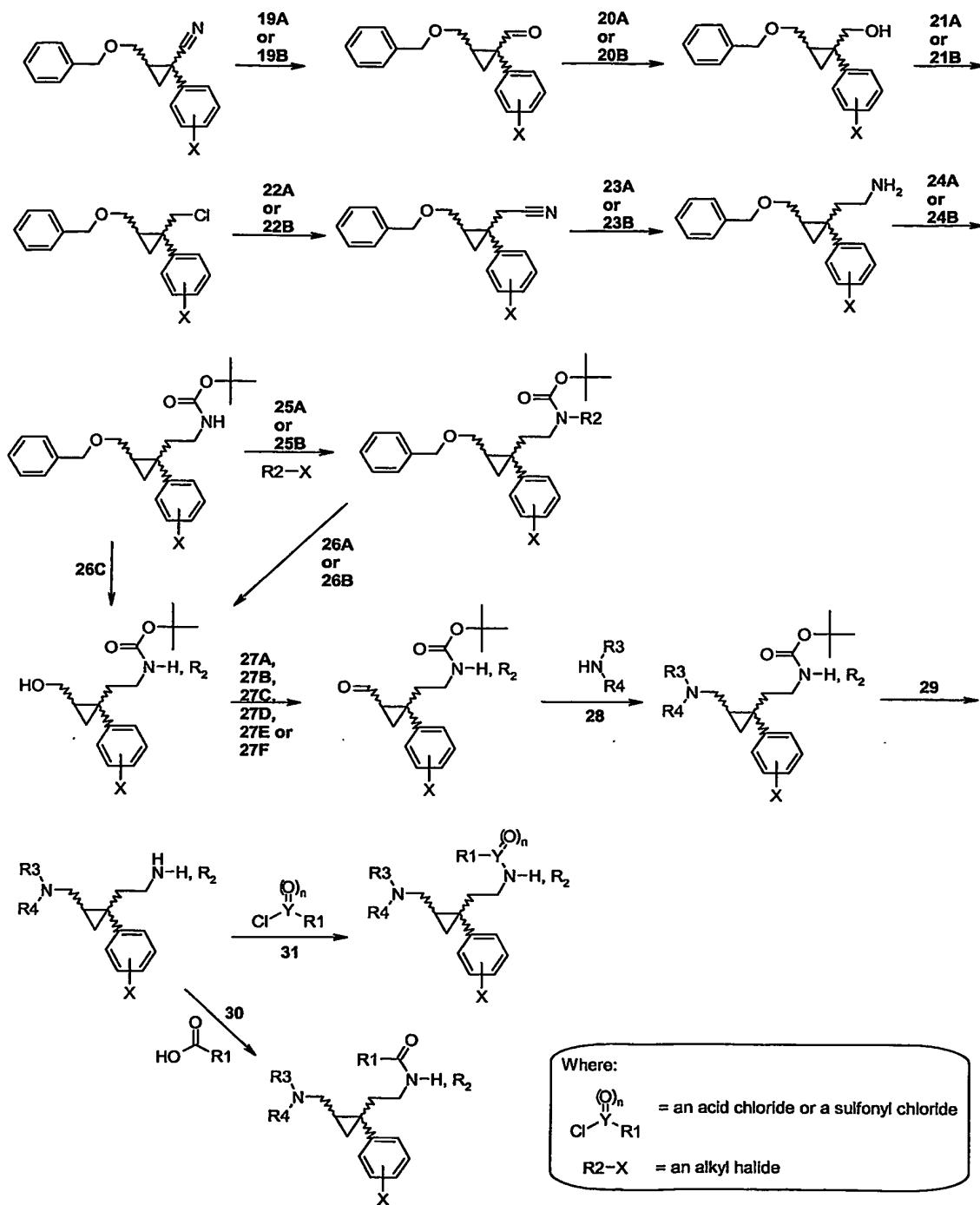
The following demonstrate the above-referenced general scheme:



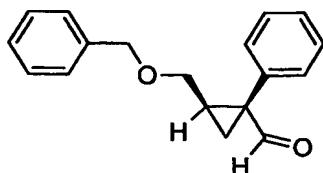
Example #	R3-N-R4	-Y(O)-R1	X	% Yield	LC/MS ES	Ion	Preparation
7			Cl		589.6, 591.5	(M+H)	18
8			Cl		543.5, 545.5	(M+H)	18
9			Cl		606.5, 608.5	(M+H)	18
10			Cl		545.5, 547.6	(M+H)	18
11			H	62	543.4	(M+H)	18

As will be appreciated by those skilled in the art, additional compounds of the present invention may be similarly prepared according to the schemes provided

5 herein.

Scheme 3:

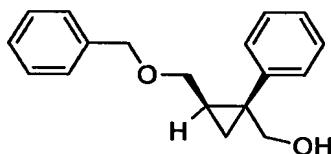
5 Preparation 19B: (1*R*,2*R*)-1-phenyl-2-
{[(phenylmethyl)oxy]methyl}cyclopropanecarbaldehyde



To a solution of 300 mL toluene and (1*R*,2*R*)-1-phenyl-2-
{[(phenylmethyl)oxy]methyl}cyclopropanecarbonitrile (12.0 g, 45.57 mmol, 1eq),

5 accessed via the method of Preparation 3B, at 0°C was added 59.3 mL 1M
diisobutylaluminum hydride (59.3 mmol, 1.3 eq) in tetrahydrofuran. The mixture was
stirred at 0°C for 4 h and then at ambient temperature for 18 h before dilution with
500 mL toluene and 500 mL water. The mixture was stirred for 30 min and then
filtered through a pad of celite. The organics were isolated, dried over Na₂SO₄,
10 filtered and concentrated to give the title compound (7.8 g, 29.3 mmol, 64%) as a
yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 9.39 (s, 1H), 7.39–7.19 (m, 10 H), 4.33–4.23
(m, 2H), 3.36–3.33 (m, 1H), 3.03–2.98 (m, 1H), 2.16–2.11 (m, 1H), 1.77–1.73 (m, 1H),
1.46–1.43 (m, 1H).

15 Preparation 20B: ((1*R*,2*R*)-1-phenyl-2-
{[(phenylmethyl)oxy]methyl}cyclopropyl)methanol

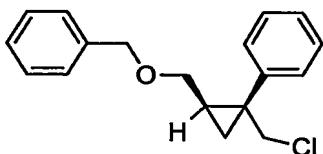


Sodium borohydride (1.2 g, 32.2 mmol, 1 eq) was added in one portion to a mixture
of (1*R*,2*R*)-1-phenyl-2-{[(phenylmethyl)oxy]methyl}cyclopropanecarbaldehyde (7.8 g,
20 29.3 mmol, 1 eq), accessed via the method of Preparation 19B, in 100mL ethyl
alcohol at ambient temperature. The reaction was stirred at ambient temperature for
18h, concentrated down and the residue partitioned between ethyl acetate and brine.
The organics were dried over Na₂SO₄, filtered and concentrated to give a yellow oil.
The crude material was purified by flash chromatography (SiO₂, eluted successively
25 with hexanes and EtOAc/hexanes (1:4)) to give the title product (7.8 g, 29.06 mmol,
99%) as a clear oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.31–7.15 (m, 10H), 4.61 (t,
J=5.7 Hz, 1H), 4.30–4.17 (m, 2H), 3.53–3.48 (m, 1H), 3.35–3.31 (m, 1H), 3.02–2.95

(m, 2H), 1.40-1.33 (m, 1H), 0.96-0.93 (m, 1H), 0.72-0.69 (m, 1H). ES-LCMS *m/z* 291.2 (M+Na).

Preparation 21B: [((1*R*,2*R*)-2-(chloromethyl)-2-

5 phenylcyclopropyl]methyl]oxy)methyl]benzene



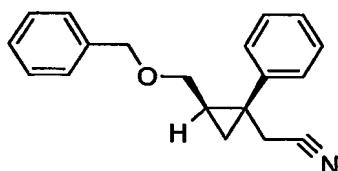
A mixture of polymer-bound triphenylphosphine (31.64 g, 67.08 mmol, 3 eq) and carbon tetrachloride (6.5 mL, 67.08 mmol, 3 eq) in 300 mL DCM was stirred at ambient temperature for 30 min. To this was added a solution of ((1*R*,2*R*)-1-phenyl-

10 2-[(phenylmethyl)oxy]methyl)cyclopropyl)methanol (6.0 g, 22.36 mmol, 1 eq), accessed via the method of Preparation 20B, in 50 mL DCM and the entire reaction mixture was stirred at ambient temperature for 16 h. The mixture was then filtered and the resin washed with excess DCM. The organics were concentrated down to give the title compound (6.4g, 22.36 mmol, 100%) as a clear oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.38-7.17 (m, 10H), 4.31-4.16 (m, 2H), 4.10-4.07 (m, 1H), 3.56-3.53 (m, 1H), 3.08-3.04 (m, 1H), 2.92-2.87 (m, 1H), 1.63-1.56 (m, 1H), 1.08-0.99 (m, 2H).

Preparation 22B: ((1*R*,2*R*)-1-phenyl-2-

15 {[(phenylmethyl)oxy]methyl)cyclopropyl)acetonitrile

20



A mixture of [((1*R*,2*R*)-2-(chloromethyl)-2-phenylcyclopropyl]methyl]oxy)methyl]benzene

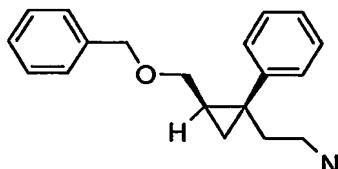
[(1*R*,2*R*)-2-(chloromethyl)-2-phenylcyclopropyl]methyl phenylmethyl diethyl ether (6.4

25 g, 22.32 mmol, 1 equiv), accessed via the method of Preparation 21B, potassium cyanide (2.18 g, 33.47 mmol, 1.5 eq) and potassium carbonate (6.17 g, 44.63 mmol, 2 eq) in 200 mL DMF was heated to 80°C for 18 h. The reaction was then partitioned between ethyl acetate and water. The organics were washed with water (3X) and brine, dried over Na₂SO₄, filtered and concentrated down. The crude material was

purified by flash chromatography (SiO_2 , eluted successively with hexanes and EtOAc/hexanes (1:4)) to give the title product (5.2 g, 18.13 mmol, 81%) as a clear oil.

^1H NMR (400 MHz, DMSO-d_6) δ 7.39-7.16 (m, 10H), 4.30-4.15 (m, 2H), 3.09-3.01 (m, 2H), 2.88-2.84 (m, 1H), 2.65-2.61 (m, 1H), 1.51-1.44 (m, 1H), 1.04-1.00 (m, 1H), 0.94-0.92 (m, 1H).

Preparation 23B: [2-((1*R*,2*R*)-1-phenyl-2-
{[(phenylmethyl)oxy]methyl}cyclopropyl)ethyl]amine



10

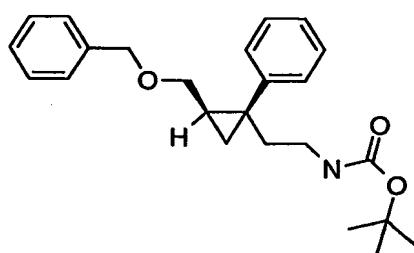
To 18.13 mL 1M lithium aluminum hydride (18.13 mmol) in diethyl ether at 0°C was added ((1*R*,2*R*)-1-phenyl-2-
{[(phenylmethyl)oxy]methyl}cyclopropyl)acetonitrile (5.2 g, 18.13 mmol), accessed via the method of Preparation 22B, dissolved in 20 mL diethyl ether. After complete addition, the reaction mixture was stirred at 0°C for 3 h.

15

The reaction mixture was diluted with 400 mL diethyl ether and quenched with successive addition of 0.6mL water, 0.6mL 15% NaOH, and 3.0mL water. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated to give the title product (5.1 g, 18.13 mmol 100%) as a clear oil. ^1H NMR (400 MHz, DMSO-d_6) δ 7.29-7.14 (m, 10H), 4.29-4.16 (m, 2H), 3.04-2.99 (m, 1H), 2.91-2.86 (m, 1H), 2.39-2.27 (m, 2H), 1.88-1.83 (m, 1H), 1.28-1.19 (m, 2H), 0.84-0.81 (m, 1H), 0.73-0.71 (m, 1H).

25

Preparation 24B: 1,1-dimethylethyl [2-((1*R*,2*R*)-1-phenyl-2-
{[(phenylmethyl)oxy]methyl}cyclopropyl)ethyl]carbamate



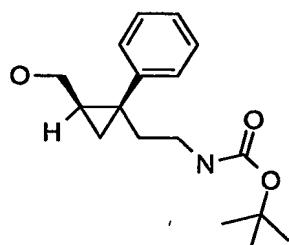
To a solution of [2-((1*R*,2*R*)-1-phenyl-2-
{[(phenylmethyl)oxy]methyl}cyclopropyl)ethyl]amine

(5.1 g, 18.12 mmol, 1eq), accessed via the method of **23B**, and triethylamine (2.78 mL, 19.03 mmol, 1.1 eq) in 75 mL DCM cooled to 0°C was added di(*tert*-butyl) dicarbonate (4.15 g, 19.03 mmol, 1.05eq). The resultant mixture was stirred 2h at 0°C followed by 16h at ambient temperature. The reaction mixture was diluted with

5 DCM, washed successively with saturated NaHCO₃ and brine, dried over MgSO₄, filtered and concentrated down. The crude material was purified by flash chromatography (SiO₂, eluted successively with hexanes and EtOAc/hexanes (1:4)) to give the title product (5.9 g, 15.46 mmol, 85%) as a clear oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.29-7.17 (m, 10H), 6.60-6.58 (m, 1H), 4.29-4.16 (m, 2H), 3.01-2.97 (m, 1H), 2.91-2.87 (m, 1H), 2.83-2.77 (m, 1H), 2.71-2.66 (m, 1H), 1.91-1.85 (m, 1H), 10 1.33-1.21 (m, 11H), 0.83-0.80 (m, 1H), 0.74-0.72 (m, 1H). ES-LCMS *m/z* 404.2 (M+Na).

Preparation 26C: 1,1-dimethylethyl {2-[(1*R*,2*R*)-2-(hydroxymethyl)-1-

15 phenylcyclopropyl]ethyl}carbamate



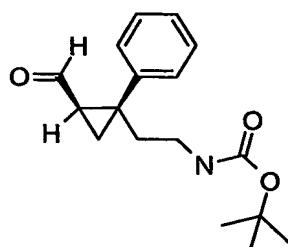
1,1-dimethylethyl [2-((1*R*,2*R*)-1-phenyl-2-
{[(phenylmethyl)oxy]methyl}cyclopropyl]ethyl]carbamate (5.9 g, 15.46 mmol),

20 accessed via the method of Preparation **24B** was combined with 10% palladium on activated carbon (600 mg) in 100 mL ethyl alcohol and hydrogenated under 1atm H₂(g) for 3h at ambient temperature. The catalyst was filtered off through celite and the filtrate concentrated to give the title compound (4.1 g, 14.07 mmol, 91 %) as a colorless oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.27-7.12 (m, 5H), 6.59-6.56 (m, 1H), 4.31-4.29 (m, 1H), 3.00-2.94 (m, 1H), 2.87-2.66 (m, 3H), 1.88-1.82 (m, 1H), 1.32-1.25 (m, 10H), 1.11-1.05 (m, 1H), 0.76-0.73 (m, 1H), 0.65-0.63 (m, 1H). ES-LCMS *m/z* 314.1 (M+Na).

Preparation 27C: 1,1-dimethylethyl {2-[(1*R*,2*R*)-2-formyl-1-

30 phenylcyclopropyl]ethyl}carbamate

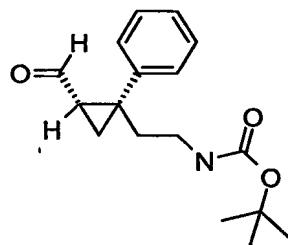
80



1,1-dimethylethyl {2-[(1*R*,2*R*)-2-(hydroxymethyl)-1-phenylcyclopropyl]ethyl}carbamate (4.1 g, 14.07 mmol), accessed via the method of Preparation 26C, was dissolved in 40 mL DCM with 1.2 mL 2-methylpropan-2-ol and treated with Dess-Martin Periodinane (9.55 g, 22.51 mmol, 1.6eq) in 40 mL DCM at ambient temperature for 3h. The reaction mixture was diluted with 50 mL diethyl ether and treated with 50 mL 1N NaOH at ambient temperature for 30min. The organic phase was separated, the aqueous phase extracted twice with diethyl ether, the organic phases combined, washed with brine, dried over MgSO₄, filtered and concentrated to a colorless oil. The crude material was purified by flash chromatography (SiO₂, eluted with EtOAc/hexanes (3:7)) to give the title compound (3.5 g, 12.10 mmol, 86%). ¹H NMR (400 MHz, CDCl₃) δ 8.43-8.41 (m, 1H), 7.31-7.20 (m, 5H), 4.41 (m, 1H), 3.04-2.95 (m, 2H), 2.16-2.10 (m, 1H), 1.99-1.94 (m, 1H), 1.88-1.85 (m, 1H), 1.54-1.46 (m, 1H), 1.38 (s, 10 H). LCMS *m/z* 312.2 (M+Na).

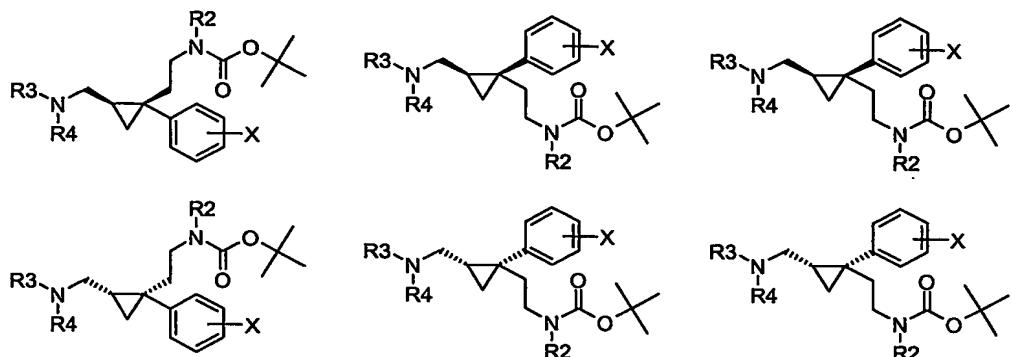
15

Preparation 27F: 1,1-dimethylethyl {2-[(1*S*,2*S*)-2-formyl-1-phenylcyclopropyl]ethyl}carbamate



Starting from (1*S*,2*S*)-1-phenyl-2-
20 {[(phenylmethyl)oxy]methyl}cyclopropanecarbonitrile, accessed via the method of 3B, and using the methods of Preparations 19B, 20B, 21B, 22B, 23B, 24B, 26C, and 27C sequentially, the title product can be obtained in comparable yields and analytical characterization to those obtained in those preparations.

Preparation 28: Compounds of generic structure:

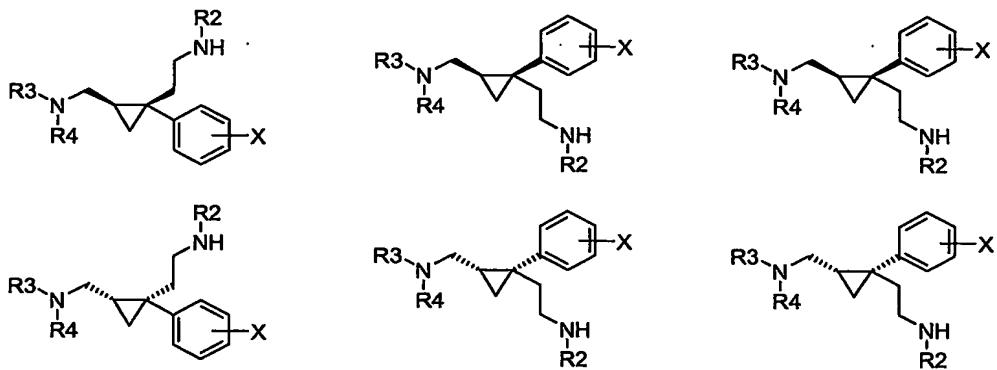


In combinatorial fashion, aldehydes prepared by the methods of Preparations 27A-F (0.35mmol) in 3mL DCE were treated with various secondary amines (0.35mmol,

5 1eq) and mp-sodium triacetoxylborohydride (500mg, 1.04mmol, 3eq) at ambient temperature for 20h with continuous agitation. The reaction mixtures were each filtered. The remaining resin was treated with 4mL DCM with agitation for 1h and the organics separated via filtration. The organic filtrates were concentrated to dryness and carried forward without purification or characterization.

10

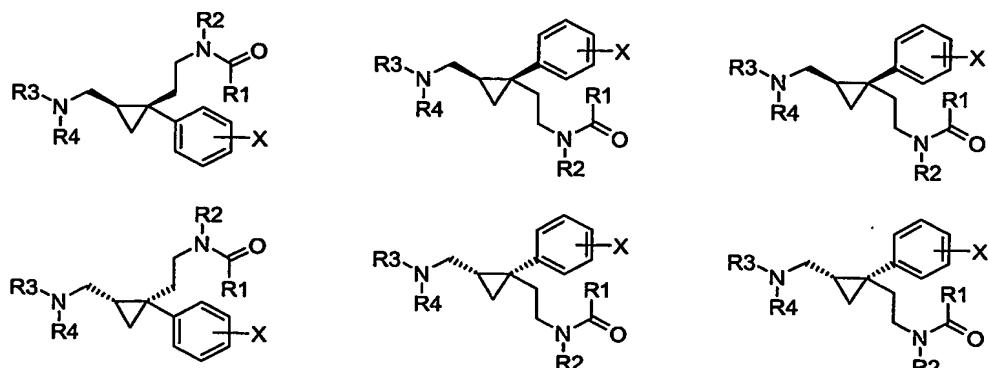
Preparation 29: Compounds of generic structure:



Compounds prepared by the method of Preparation 28 were treated with 1mL trifluoroacetic acid in 2mL DCM and 2mL DCE for 5h at ambient temperature with

15 slight agitation. The reaction mixtures were concentrated and partitioned between DCM (2mL) and saturated NaHCO₃ (2mL) and the organic phases separated via filtration through hydrophobic frit tube assemblies. The organic filtrates were concentrated to dryness and carried forward without purification or characterization.

Preparation 30: Compounds of general formula:



The compounds prepared according to the method of Preparation 29 were dissolved in 3mL DCE and further split out in combinatorial fashion such that each reaction was

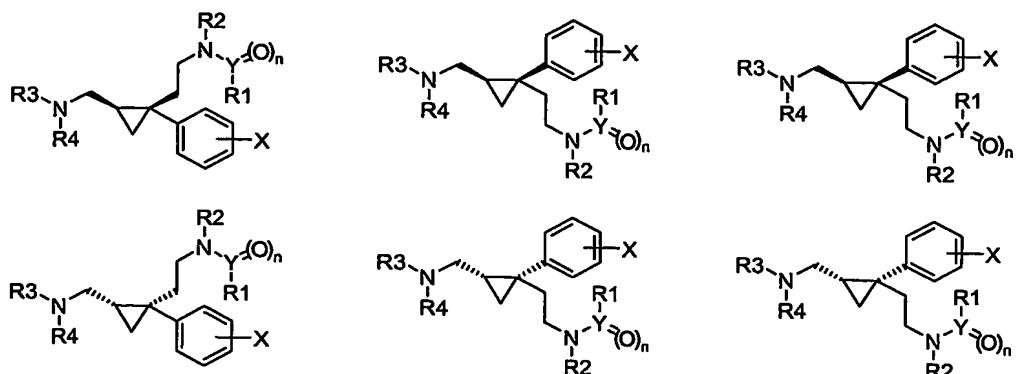
5 performed on a theoretical scale of 0.12mmol in 1mL DCE. The reaction plates were concentrated down and the residues taken up in 1mL DMF for reaction. Polymer-bound diisopropylamine (0.48mmol, 4eq) was added to each well followed by an acid (0.13mmol, 1.1eq) in 0.5mL DMF and HATU (0.12mmol, 1eq) in 0.5 mL DMF. The resultant reaction mixtures were agitated at ambient temperature for 18h and HATU

10 byproducts scavenged by addition of polymer-bound carbonate (0.36mmol, 3eq) and agitation at ambient temperature for 3h. The reaction plates were filtered and the filtrates concentrated to dryness. Crude products were dissolved in 300 microliters of DMSO and brought up to a final volume of 500 microliters using methanol. This 500 microliter solution was injected by a Waters 2767 autosampler into an XTerra C18 5

15 micron particle HPLC column (19mmX150mm). Initial solvent flow was 20ml/min with 30% methanol and 70% water at a pH of 11 using ammonium hydroxide as buffer. Void volume was 2 minutes, and a linear gradient to 100% methanol in 10 minutes with a five minute wash at 100% methanol eluted the compound in approximately 10 minutes. A Micromass Platform LC mass spectrometer was used

20 to monitor a split off the eluate for desired mass, and the purified fractions were collected using Micromass Fractionlynx software. Chiral HPLC was performed on representative samples to confirm that homochiral integrity had been preserved.

Preparation 31: Compounds of general formula:



The compounds prepared according to the method of Preparation 29 were dissolved in 3mL DCE (1:1) and further split out in combinatorial fashion such that each

5 reaction was performed on a theoretical scale of 0.12mmol in 1mL DCE. Polymer-bound diisopropylamine (0.48mmol, 4eq) was added to each well followed by either an acid chloride or sulfonyl chloride (0.12mol, 1eq) in 1mL DCE. The resultant reaction mixtures were agitated at ambient temperature for 16h and excess acid or sulfonyl chloride scavanged by addition of polymer-bound trisamine (0.36mmol, 3eq)

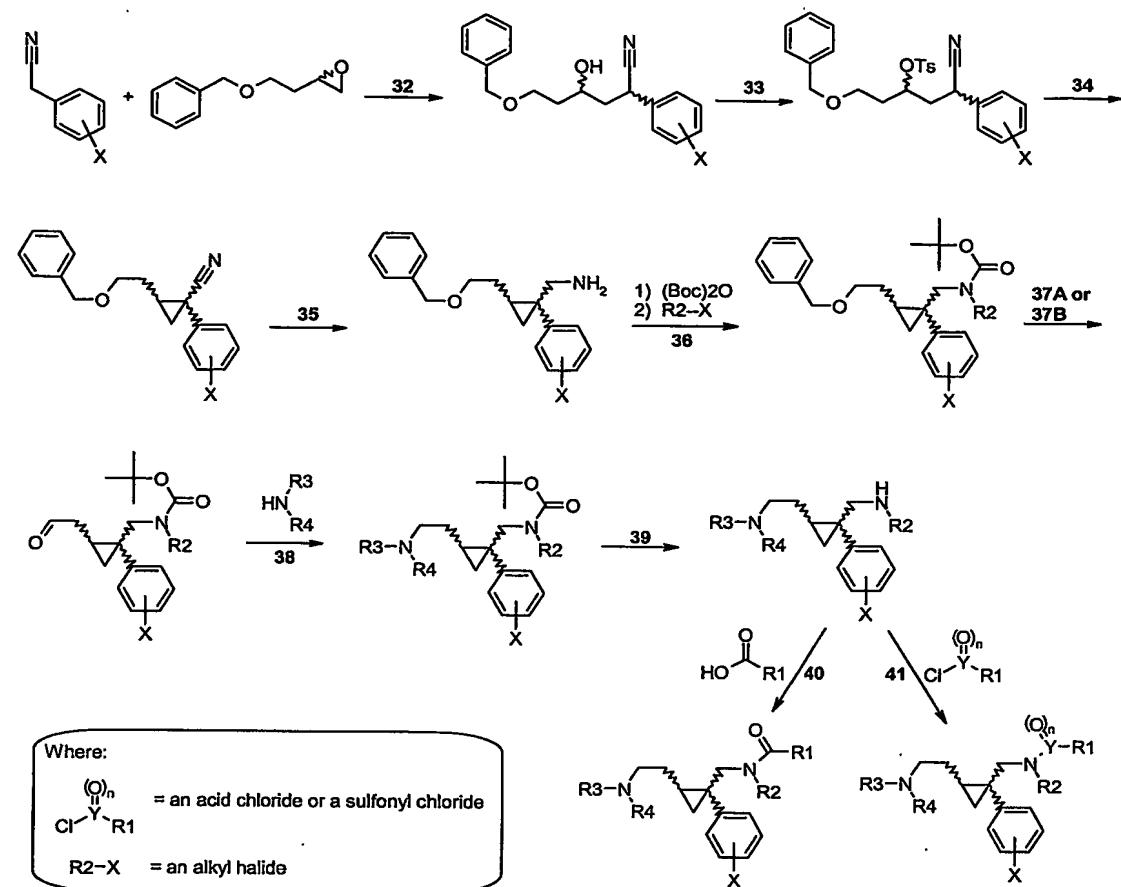
10 and agitation at ambient temperature for 4h. The reaction plates were filtered and the filtrates concentrated to dryness. Crude products were dissolved in 300 microliters of DMSO and brought up to a final volume of 500 microliters using methanol. This 500 microliter solution was injected by a Waters 2767 autosampler into an XTerra C18 5 micron particle HPLC column (19mmX150mm). Initial solvent

15 flow was 20ml/min with 30% methanol and 70% water at a pH of 11 using ammonium hydroxide as buffer. Void volume was 2 minutes, and a linear gradient to 100% methanol in 10 minutes with a five minute wash at 100% methanol eluted the compound in approximately 10 minutes. A Micromass Platform LC mass spectrometer was used to monitor a split off the eluate for desired mass, and the

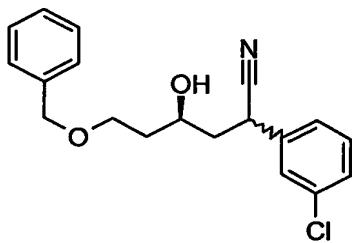
20 purified fractions were collected using Micromass Fractionlynx software. Chiral HPLC was performed on representative samples to confirm that homochiral integrity had been preserved.

84

Scheme 4:



Preparation 32: (4S)-2-(3-chlorophenyl)-4-hydroxy-6-[(phenylmethyl)oxy]hexanenitrile



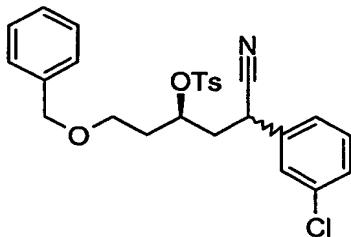
5 (3-Chlorophenyl)acetonitrile (8.62 mL, 72.9 mmol) in 100mL of THF was cooled to -78°C . Butyllithium (35.1 mL, 56.1 mmol, 1.6 M in THF) was added over 20 minutes and stirred for an additional 15 min at -78°C . (2*R*)-2-{[(phenylmethyl)oxy]ethyl}oxirane (10.0 g, 56.1 mmol, *Synthesis* **1992**, 7, 621-623) in 20 mL of THF was added over 30 minutes and stirred for an additional hour at -78°C .

10 After warming to room temperature the solvent was evaporated and the orange red oil was chromatographed on silica gel with 20-25% EtOAc in Hexanes to give the title

compound (11.05g, 58%). ^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.8 (m, 3 H) 3.6 (m, 1 H) 3.7 (m, 2 H) 4.1 (m, 2 H) 4.5 (m, 2 H) 7.3 (m, 9 H).

Preparation 33: (1*S*)-3-(3-chlorophenyl)-3-cyano-1-{2-

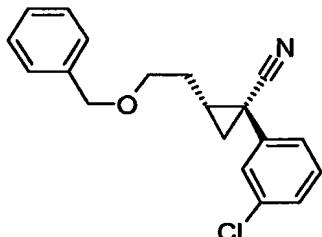
5 [(phenylmethyl)oxy]ethyl}propyl 4-methylbenzenesulfonate



To a solution of (4*S*)-2-(3-chlorophenyl)-4-hydroxy-6-[(phenylmethyl)oxy]hexanenitrile (6.00 g, 18.2 mmol) in 50% CHCl_3 in pyridine at 0°C was added DMAP (2.22 g) and toluenesulfonyl chloride (10.4 g, 54.5 mmol). After warming to room temperature

10 over several hours, the reaction mixture was stored in the freezer for 2 days. After an aqueous work up with 1N HCl the organic layer was dried over MgSO_4 and evaporated to an oil. Chromatography on silica with 25% EtOAc in Hexanes afforded the title compound (5.68 g, 66%) as a yellow oil. ^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.9 (m, 2 H) 2.1 (m, 2 H) 2.3 (m, 2 H) 2.4 (s, 3 H) 3.4 (m, 1 H) 3.5 (m, 1 H) 4.4 (m, 2 H) 7.1 (m, 1 H) 7.3 (m, 10 H) 7.8 (m, 2 H)

Preparation 34: (1*R*,2*R*)-1-(3-chlorophenyl)-2-{2-[(phenylmethyl)oxy]ethyl}cyclopropanecarbonitrile



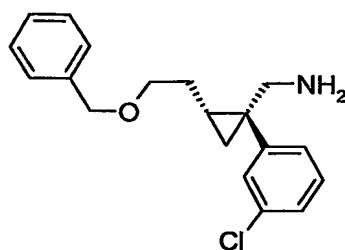
20

3.2 mL 1M LHMDS in hexanes (3.2 mmol) was added to 15 mL of DMF and cooled to -40°C. To this was added a solution of (1*S*)-3-(3-chlorophenyl)-3-cyano-1-{2-[(phenylmethyl)oxy]ethyl}propyl 4-methylbenzenesulfonate (1.00 g, 2.12 mmol) in 5 mL of DMF over 10 minutes and stirred for 40 minutes. After warming to room

25 temperature the reaction was stirred until no starting material remained by TLC. The reaction mixture was poured into 100 mL water, extracted with 50mL EtOAc, the

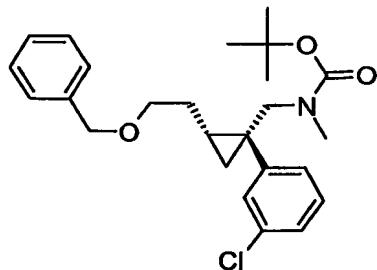
organic phase isolated, washed with brine and dried over MgSO_4 . The resulting residue was purified by silica gel chromatography with 25% EtOAc in hexanes to give the title compound (436 mg, 65% yield). ^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.4 (dd, $J=7.5, 5.6$ Hz, 1 H) 1.5 (m, 1 H) 1.7 (m, 1 H) 2.0 (m, 2 H) 3.6 (m, 2 H) 5 4.5 (d, $J=2.2$ Hz, 2 H) 7.1 (m, 1 H) 7.2 (m, 3 H) 7.3 (m, 5 H).

Preparation 35: $[(1R,2R)-1-(3\text{-chlorophenyl})-2\text{-}\{2\text{-}\}[(\text{phenylmethyl})\text{oxy}]\text{ethyl}\}\text{cyclopropyl}]\text{methyl}\text{amine}$



10 A solution of $(1R,2R)-1-(3\text{-chlorophenyl})-2\text{-}\{2\text{-}\}[(\text{phenylmethyl})\text{oxy}]\text{ethyl}\}\text{cyclopropanecarbonitrile}$ (1.26 g, 4.0 mmol) in diethyl ether at 0°C was treated with 2 equivalents of LAH (1M in diethyl ether). After 1.5 hours at 0°C , water was added dropwise until no further evolution of gas was observed. The aluminum salts were filtered off and washed with diethyl ether. Evaporation of the diethyl ether afforded the title compound. ^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.5 (dd, $J=5.9, 4.8$ Hz, 1 H) 1.0 (dd, $J=8.9, 4.7$ Hz, 1 H) 1.2 (m, 1 H) 1.4 (s, 2 H) 1.8 (m, 2 H) 2.9 (m, 2 H) 3.6 (m, 2 H) 4.6 (s, 2 H) 7.2 (m, 3 H) 7.3 (m, 2 H) 7.4 (m, 4 H) .

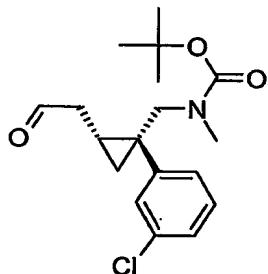
15 20 Preparation 36: 1,1-dimethylethyl $[(1R,2R)-1-(3\text{-chlorophenyl})-2\text{-}\{2\text{-}\}[(\text{phenylmethyl})\text{oxy}]\text{ethyl}\}\text{cyclopropyl}]\text{methyl}\text{carbamate}$



25 A solution of $[(1R,2R)-1-(3\text{-chlorophenyl})-2\text{-}\{2\text{-}\}[(\text{phenylmethyl})\text{oxy}]\text{ethyl}\}\text{cyclopropyl}]\text{methyl}\text{amine}$ (1.67 g, 5.29 mmol) and

triethylamine (0.74 mL, 5.29 mmol) in DCM was cooled to 0°C. Di-*tert*-butyl dicarbonate (1.15 g, 5.29 mmol) was added as a solid and stirred at 0°C for 1 hour. The reaction mixture was evaporated to give 2.27 g of an oil which was redissolved in THF and iodomethane (2.27 g, 15.98 mmol) and cooled to 0 C°. NaHMDS (8.0 mL, 1M in THF) was added over 20 minutes to the stirring solution. After warming to room temperature the reaction was poured into water and diethyl ether. The diethyl ether was isolated, washed with water, dried over MgSO₄ and evaporated to afford the title compound (2.08 g, 91% yield). ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.7 (m, 1 H) 1.2 (m, 9 H) 1.3 (m, 3 H) 1.7 (m, 1 H) 1.9 (m, 1 H) 2.6 (s, 1 H) 2.8 (s, 2 H) 3.6 (m, 2 H) 3.9 (d, *J*=14.8 Hz, 1 H) 4.6 (s, 2 H) 7.2 (m, 3 H) 7.3 (m, 2 H) 7.3 (m, 4 H)

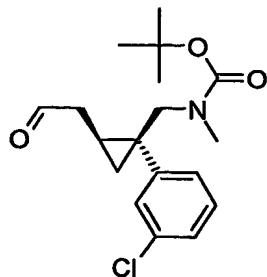
Preparation 37A: 1,1-dimethylethyl {[*(1R,2R)*-1-(3-chlorophenyl)-2-(2-oxoethyl)cyclopropyl]methyl}methylcarbamate



15

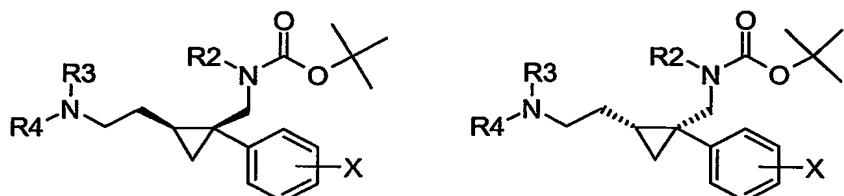
A solution of 1,1-dimethylethyl {[*(1R,2R)*-1-(3-chlorophenyl)-2-[2-[(phenylmethyl)oxy]ethyl]cyclopropyl)methyl}methylcarbamate (2.08 g, 4.83mmole) in 50 mL EtOAc was stirred overnight under 1 atmosphere of H₂ with 360 mg of 10% Pd on carbon. The suspension was filtered through celite and evaporated to afford 1.84 g of an oil. The oil was dissolved in DCM and added to a solution of Dess-Martin periodinane (3.67 g, 8.66 mmol) and 2-methyl-2-propanol (828 μl, 8.66mmole) in DCM. After stirring overnight, the reaction mixture was mixed with 100 mL of 1N NaOH and 5.0 g of Na₂SO₄ for 20 minutes. 100 mL of diethyl ether was added and the organic layer washed with 1N NaOH, water and dried over MgSO₄. Removal of solvent afforded the title compound as a crude oil which was used without further purification. ES-LCMS *m/z* 360 (M+Na).

Preparation 37B: *tert*-butyl {[*(1R,2S)*-1-(3-chlorophenyl)-2-(2-oxoethyl)cyclopropyl]methyl}methylcarbamate



Starting from (3-chlorophenyl)acetonitrile and (2*S*)-2-{2-[(phenylmethyl)oxy]ethyl}oxirane and using the methods of Preparations 32, 33, 34, 35, 36, and 37A sequentially, the title product can be obtained in comparable yields and analytical characterization to those obtained in those preparations.

Preparation 38: Compounds of generic structure:

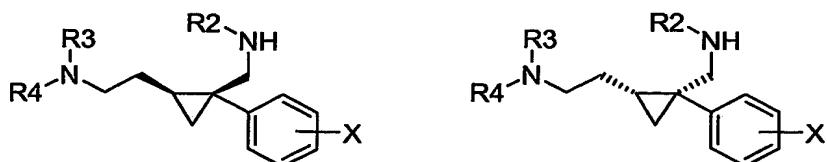


In combinatorial fashion, aldehydes prepared by the method of Preparations 37A-B

10 (0.35mmol) in 3mL DCE were treated with various secondary amines (0.35mmol, 1eq) and mp-sodium triacetoxyborohydride (500mg, 1.04mmol, 3eq) at ambient temperature for 20h with continuous agitation. The reaction mixtures were each filtered. The remaining resin was treated with 4mL DCM with agitation for 1h and the organics separated via filtration. The organic filtrates were concentrated to dryness

15 and carried forward without purification or characterization.

Preparation 39: Compounds of generic structure:

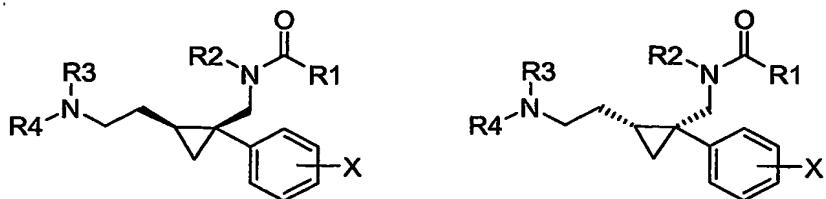


Compounds prepared by the method of Preparation 38 were treated with 1mL

20 trifluoroacetic acid in 2mL DCM and 2mL DCE for 5h at ambient temperature with slight agitation. The reaction mixtures were concentrated and partitioned between DCM (2mL) and saturated NaHCO₃ (2mL) and the organic phases separated via

filtration through hydrophobic frit tube assemblies. The organic filtrates were concentrated to dryness and carried forward without purification or characterization.

Preparation 40: Compounds of general formula:

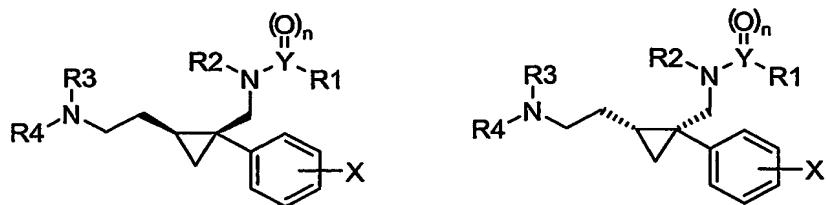


5

The compounds prepared according to the method of Preparation 39 were dissolved in 3mL DCE and further split out in combinatorial fashion such that each reaction was performed on a theoretical scale of 0.12mmol in 1mL DCE. The reaction plates were concentrated down and the residues taken up in 1mL DMF for reaction. Polymer-

10 bound diisopropylamine (0.48mmol, 4eq) was added to each well followed by an acid (0.13mmol, 1.1eq) in 0.5mL DMF and HATU (0.12mmol, 1eq) in 0.5 mL DMF. The resultant reaction mixtures were agitated at ambient temperature for 18h and HATU byproducts scavenged by addition of polymer-bound carbonate (0.36mmol, 3eq) and agitation at ambient temperature for 3h. The reaction plates were filtered and the
 15 filtrates concentrated to dryness. Crude products were dissolved in 300 microliters of DMSO and brought up to a final volume of 500 microliters using methanol. This 500 microliter solution was injected by a Waters 2767 autosampler into an XTerra C18 5 micron particle HPLC column (19mmX150mm). Initial solvent flow was 20ml/min with 30% methanol and 70% water at a pH of 11 using ammonium hydroxide as
 20 buffer. Void volume was 2 minutes, and a linear gradient to 100% methanol in 10 minutes with a five minute wash at 100% methanol eluted the compound in approximately 10 minutes. A Micromass Platform LC mass spectrometer was used to monitor a split off the eluate for desired mass, and the purified fractions were collected using Micromass Fractionlynx software. Chiral HPLC was performed on
 25 representative samples to confirm that homochiral integrity had been preserved.

Preparation 41: Compounds of general formula:



The compounds prepared according to the method of Preparation 39 were dissolved in 3mL DCE (1:1) and further split out in combinatorial fashion such that each

5 reaction was performed on a theoretical scale of 0.12mmol in 1mL DCE. Polymer-bound diisopropylamine (0.48mmol, 4eq) was added to each well followed by either an acid chloride or sulfonyl chloride (0.12mol, 1eq) in 1mL DCE. The resultant reaction mixtures were agitated at ambient temperature for 16h and excess acid or sulfonyl chloride scavanged by addition of polymer-bound trisamine (0.36mmol, 3eq)

10 and agitation at ambient temperature for 4h. The reaction plates were filtered and the filtrates concentrated to dryness. Crude products were dissolved in 300 microliters of DMSO and brought up to a final volume of 500 microliters using methanol. This 500 microliter solution was injected by a Waters 2767 autosampler into an XTerra C18 5 micron particle HPLC column (19mmX150mm). Initial solvent

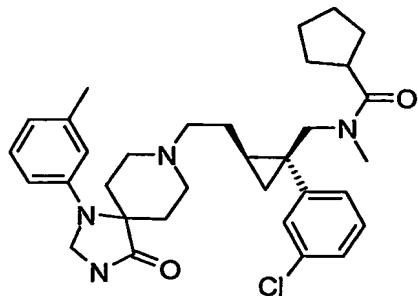
15 flow was 20ml/min with 30% methanol and 70% water at a pH of 11 using ammonium hydroxide as buffer. Void volume was 2 minutes, and a linear gradient to 100% methanol in 10 minutes with a five minute wash at 100% methanol eluted the compound in approximately 10 minutes. A Micromass Platform LC mass spectrometer was used to monitor a split off the eluate for desired mass, and the

20 purified fractions were collected using Micromass Fractionlynx software. Chiral HPLC was performed on representative samples to confirm that homochiral integrity had been preserved.

The following example demonstrates the above-referenced general scheme:

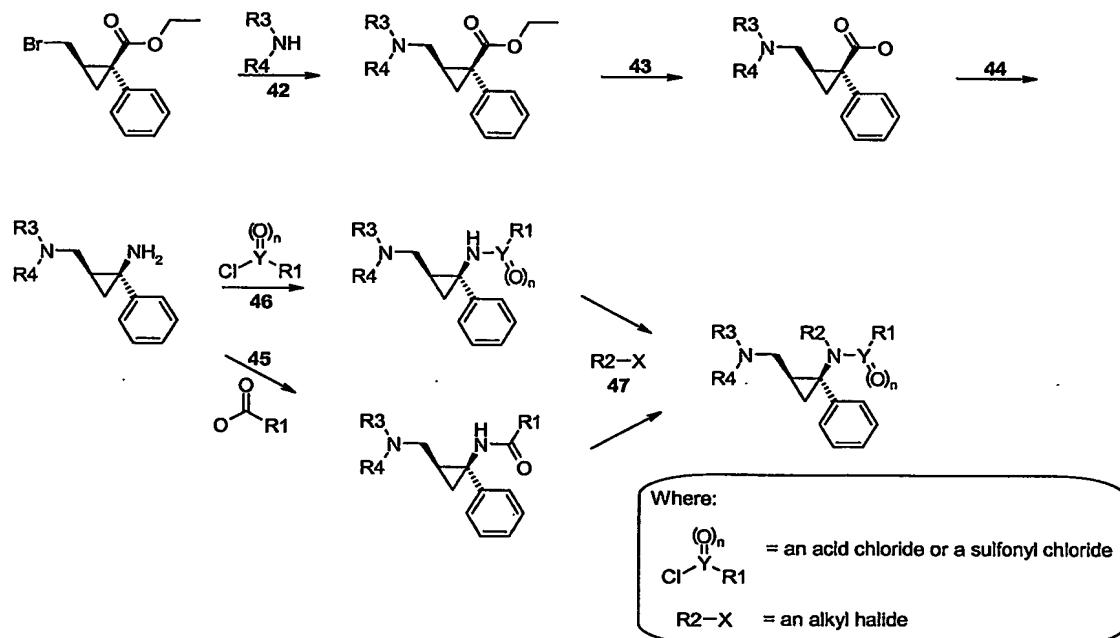
25

Example 12: *N*-[((1*S*,2*S*)-1-(3-chlorophenyl)-2-{2-[1-(3-methylphenyl)-4-oxo-1,3,8-triazaspiro[4.5]dec-8-yl]ethyl}cyclopropyl)methyl]-*N*-methylcyclopentanecarboxamide

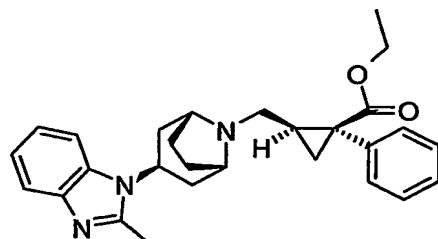


The title compound was prepared according to the methods of Preparation 41. ES-LCMS m/z 661.36 (M+H).

5 Scheme 5:



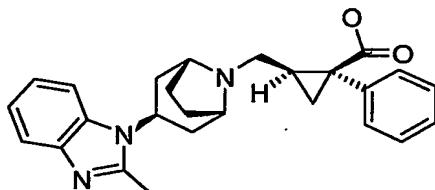
Preparation 42: Ethyl (1*S*,2*R*)-2-[(3-*endo*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]methyl]-1-phenylcyclopropanecarboxylate



10 **Ethyl (1*S*,2*R*)-2-(bromomethyl)-1-phenylcyclopropanecarboxylate** (538mg, 1.90mmol, 1eq., *J. Med. Chem.* 1987, 30(2), 318-325) was combined with 1-[(3-*endo*)-8-

azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole (700mg, 1.90mmol, 1eq., WO 00/38680), potassium carbonate (790mg, 5.70mmol, 3eq.) and a catalytic amount of potassium iodide in 10mL DMF and stirred 16h at 85°C. The reaction mixture was partitioned between EtOAc and water (pH = 9) and the organic phase isolated. The 5 organic phase was combined with fresh water and the pH adjusted to 2 with 1N HCl. The aqueous phase was isolated, the pH adjusted to 11 with 1N NaOH, and extracted with DCM. The organic phase was isolated, dried over MgSO₄, filtered and concentrated to give the title compound (574mg, 1.29mmol, 68%) as a brown foam. ¹H NMR (400 MHz, DMSO-D₆, 85°C) δ ppm 1.2 (t, *J*=7.1 Hz, 3 H) 1.4 (dd, 10 *J*=9.0, 4.5 Hz, 1 H) 1.6 (dd, *J*=7.1, 4.5 Hz, 1 H) 1.8 (m, 3 H) 1.9 (m, 2 H) 2.1 (m, 2 H) 2.4 (m, 2 H) 2.5 (s, 3 H) 2.7 (m, 1 H) 3.4 (m, 1 H) 3.7 (m, 1 H) 4.1 (q, *J*=7.1 Hz, 2 H) 4.8 (m, 1 H) 7.1 (m, 2 H) 7.2 (m, 1 H) 7.3 (t, *J*=7.4 Hz, 2 H) 7.4 (m, 2 H) 7.4 (m, 1 H) 7.5 (m, 1 H). ES-LCMS *m/z* 444.24 (M+H).

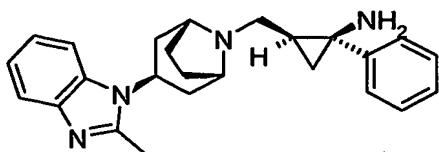
15 Preparation 43: (1*S*,2*R*)-2-{{(3-*endo*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]methyl}-1-phenylcyclopropanecarboxylic acid



Ethyl (1*S*,2*R*)-2-{{(3-*endo*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]methyl}-1-phenylcyclopropanecarboxylate (574mg, 1.29mmol, 1eq.) was 20 dissolved in 1.9mL ethyl alcohol and treated with 1.9mL 1N LiOH (1.9mmol, 1.5eq.) 16h at ambient temperature. The reaction mixture was concentrated to dryness, chased three times with toluene and pumped on under high vacuum to dryness. The crude product was triturated with DCM which was decanted off leaving the title compound (526mg, 1.27mmol, 99%) as a white solid residue. ¹H NMR (400 MHz, 25 DMSO-D₆, 85°C) δ ppm 1.3 (dd, *J*=8.9, 4.4 Hz, 1 H) 1.5 (dd, *J*=7.0, 4.4 Hz, 1 H) 1.7 (m, 3 H) 1.9 (m, 2 H) 2.2 (m, 2 H) 2.5 (m, 2 H) 2.5 (s, 3 H) 2.7 (dd, *J*=12.8, 5.4 Hz, 1 H) 3.4 (m, 1 H) 3.7 (m, 1 H) 4.9 (m, 1 H) 7.1 (m, 2 H) 7.2 (m, 1 H) 7.3 (m, 2 H) 7.4 (m, 2 H) 7.4 (m, 1 H) 7.5 (m, 1 H). ES-LCMS *m/z* 416.19 (M+H).

30 Preparation 44: ((1*S*,2*S*)-2-{{(3-*endo*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]methyl}-1-phenylcyclopropyl)amine

93

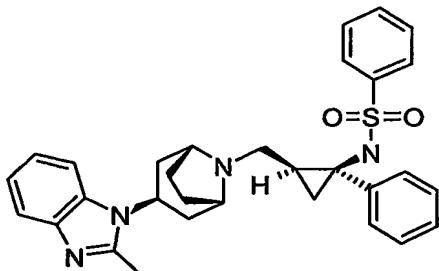


(1*S*,2*R*)-2-[(3-*endo*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]methyl]-1-phenylcyclopropanecarboxylic acid (174mg, 0.42mmol, 1eq.) was treated with 10mL thionyl chloride for 16h at ambient temperature. The reaction

5 mixture was concentrated to dryness, chased two times with toluene and pumped dry to give the acid chloride as a yellow foam. The acid chloride thus obtained was suspended in 5mL acetone and treated with sodium azide (73mg, 1.12mmol, 2.7eq.) dissolved in 2mL water at ambient temperature. The reaction mixture was stirred 1h at ambient temperature and then diluted with saturated NaHCO₃ and extracted with
 10 toluene. The toluene layer was isolated, dried over MgSO₄, filtered, and the filtrate heated at 90°C for 2h. After cooling, water was added to the reaction mixture and the pH adjusted to 2 with 1N HCl. The aqueous phase was isolated, the pH adjusted to 10 with 1N NaOH, extracted two times EtOAc, the organic phases combined, dried over MgSO₄, filtered and concentrated to give the title compound (61mg, 0.16mmol,
 15 38%) as a yellow film. ¹H NMR (400 MHz, DMSO-D₆, 85°C) δ ppm 0.7 (m, 1 H) 1.2 (m, 2 H) 1.7 (m, J=7.6 Hz, 2 H) 1.9 (m, 2 H) 2.2 (m, 2 H) 2.4 (m, J=8.6 Hz, 2 H) 2.5 (m, 3 H) 2.6 (m, 2 H) 3.5 (m, 1 H) 3.6 (m, 1 H) 4.7 (m, 1 H) 7.1 (m, 3 H) 7.3 (t, J=7.8 Hz, 2 H) 7.4 (m, 2 H) 7.4 (d, J=7.4 Hz, 1 H) 7.5 (d, J=8.3 Hz, 1 H). ES-LCMS *m/z* 387.28 (M+H).

20

Preparation 46, Example 13: *N*-((1*S*,2*S*)-2-[(3-*endo*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]methyl)-1-phenylcyclopropyl)benzenesulfonamide

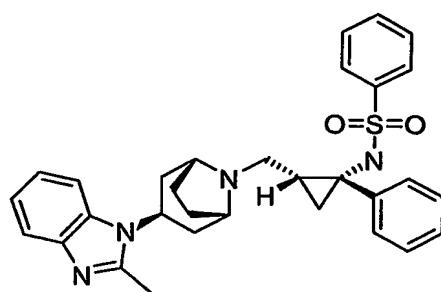


((1*S*,2*S*)-2-[(3-*endo*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]methyl)-1-phenylcyclopropyl)amine (40mg, 0.103mmol, 1eq.) was dissolved in 2mL DCM/DCE (1:1) and treated with benzenesulfonyl chloride (40uL, 0.310mmol, 3eq.) in the presence of PS-DIEA (40mg, 0.155mmol, 1.5eq) at ambient temperature for

3h. The resin was filtered off and the filtrate concentrated to dryness. The crude product was purified by HPLC on a C-18 column eluted with 0→100%CH3CN in water buffered with 0.1% TEA. The appropriate fraction was isolated and concentrated to give the title compound (20mg, 0.038mmol, 37%) as a white solid.

5 ^1H NMR (400 MHz, DMSO-D6, 85°C) δ ppm 1.2 (m, 2 H) 1.5 (m, 1 H) 1.7 (m, 2 H) 1.9 (m, 2 H) 2.0 (m, 2 H) 2.2 (dd, J =12.9, 6.5 Hz, 1 H) 2.4 (m, 2 H) 2.5 (s, 3 H) 2.6 (dd, J =12.5, 5.0 Hz, 1 H) 3.4 (m, 1 H) 3.5 (m, 1 H) 4.7 (m, 1 H) 7.1 (m, 5 H) 7.2 (m, 2 H) 7.4 (m, 3 H) 7.5 (m, 2 H) 7.6 (m, 2 H) 8.4 (s, 1 H). ES-LCMS m/z 527.27 (M+H).

10 Example 14: *N*-(*(1R,2R*)-2-*{[(3-endo)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]methyl*}-1-phenylcyclopropyl)benzenesulfonamide



Starting from ethyl (*1R,2S*)-2-(bromomethyl)-1-phenylcyclopropanecarboxylate (*J. Med. Chem.* 1987, 30(2), 318-325) and using the methods of Preparations 42, 43, 44 and 46 sequentially, the title product can be obtained in comparable yields and analytical characterization to those obtained in those preparations.

List of abbreviations:

LAH = lithium aluminum hydride

20 DCE = dichloroethane

TFA = trifluoroacetic acid

LDA = lithium diisopropylamide

TEA = triethylamine

THF = tetrahydrofuran

25 DCM = dichloromethane

TLC = thin layer chromatography

LHMDS = lithium bis(trimethylsilyl)amide

NaHMDS = sodium bis(trimethylsilyl)amide

PS-DIEA = polystyrene supported diisopropylethylamine

PS-Trisamine = polystyrene supported trisamine

HATU = *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate

DMF = *N,N*-Dimethylformamide

5 DMSO = Dimethyl sulfoxide

DIEA = *N,N*-Diisopropylethylamine

THF = Tetrahydrofuran

NaBH(OAc)₃ = sodium triacetoxyborohydride

EtOAc = ethyl acetate

10 DMAP = dimethylaminopyridine

h = hours

HPLC = high performance liquid chromatography

SiO₂ = silica gel

15 As will be appreciated by those skilled in the art, additional compounds of the present invention may be similarly prepared according to the schemes provided herein.

BIOLOGICAL DATA

20 The following definitions apply:

IC ₅₀	Concentration of compound that displaces 50% of radioligand
pIC ₅₀	The determined IC ₅₀ value expressed as -log ₁₀ (IC ₅₀)

CC-Chemokine Receptor-5 Binding by Scintillation Proximity Assay (CCR5 SPA)
Scintillation Proximity Assay for the Human CC-Chemokine Receptor, CCR-5

25

This protocol describes a high-throughput screen using SPA binding to identify compounds that inhibit binding of ¹²⁵I-MIP1 α to the human CCR5 chemokine receptor.

30 CCR5 is a G protein-coupled receptor that binds the natural chemokine ligands, MIP1 α , MIP1 β and RANTES. CCR5 acts as a co-receptor with CD4 for entry of HIV-1 into human T-cells and monocytes. Chemokines also play a role in acute and chronic inflammatory processes. Chemokines are soluble proteins produced and

released by a wide variety of cell types during the initial phase of a host response to a forgein substance entering the body.

Human CCR5 receptors were expressed in Chinese Hamster Ovary (CHO) cells,

- 5 registration # 12025. Cells were grown in suspension and a 50 to 80 ml CCR5 cell pellet was prepared. Membrane preparation: 1) Weigh pellet; 2)Prepare an ice-cold 50mM HEPES buffer, containing 0.0025mg/ml Pefabloc, 0.0001mg/ml Pepstatin A, 0.0001mg/ml Leupeptin, 0.0001mg/ml Aprotinin (protease inhibitor cocktail), pH 7.4; 3) Homogenize pellet in 5 volumes of HEPES buffer; 4) Homogenize again with a
- 10 glass homogenizer 10 to 20 strokes; 5) Centrifuge homogenate at 18,000 rpm in a F28/36 rotor using a Sorvall RC26 PIUS refrigerated Centrifuge for 30 minutes; 6) Discard supernatant and resuspend pellet in 3 volumes of HEPES buffer; 7) Homogenize and centrifuge again using steps 4-6, 2 more times; 8) Reweigh pellet and homogenize in 3X weight-to-volume of HEPES buffer; 9) Aliquot 0.5 to 1.5ml of
- 15 the membrane preparation into small vials and store at -80 degrees Centigrade; 10) Determine the protein concentration of the membrane preparation using the Bio-Rad or BCA method; 11) The membrane homogenate will need to be characterized for the assay conditions a.) Protein concentration; b.) Optimal protein-to-bead ratio in SPA; and c.) Saturation curve to determine Kd and Bmax in SPA

20

The saturation curve binding experiment is performed by adding varying amounts of [¹²⁵I]MIP1 α (0-8.5nM to membranes and beads in concentrations chosen from the optimal protein/bead ratio. The data is analyzed using a non-linear curve-fitting program. The K_d and Bmax are derived from the curve.

25

Bacitracin 50mg/ml is dissolved in deionized water, brought to a boil for 5 minutes (to destroy protease activity) and cooled. Prepared 1ml aliquots and store at -80°C.

- 30 Protease inhibitor cocktail is prepared by dissolving 25 mg/ml of Pefabloc, 1 mg/ml of Leupeptin, 1 mg/ml of Aprotinin and 1mg/ml of Pepstatin A in 100% DMSO. The cocktail can be aliquoted and stored frozen at -20°C until needed.

Sigmacote: Any reagent bottles and reservoirs that come in contact with the radioligand are treated with Sigmacote to reduce sticking. Rinse containers with

undiluted Sigmacote; rinse with deionized water several times, and allow to air dry before using.

Color Quench Assay- [¹²⁵I] SPA PVT color quench kit, Cat. No. RPAQ 4030,

5 Amersham Ltd. A color quench curve is generated for each Packard TopCount and is stored in each counting protocol specific for the assay. This is done to prevent colored compounds from quenching the scintillation counts.

Compounds Preparation:

10 Compounds for a single concentration determination (One Shots) are delivered in 96 well Packard Optiplates containing 1 μ l of compound in 100% DMSO in columns A1-H10 (80 compounds/plate). Column A11 to H11 is used for total binding (Bo) (vehicle-5 μ l of the appropriate DMSO concentration) and column A12 to D12 is used for determination of nonspecific binding. No further preparation is required.

15 Compounds for concentration-response curves (10 points) are delivered in 96-Packard Optiplates containing 1 μ l of compound in 100% DMSO in columns A1-H10. A 10-point concentration-response curve is desired for each compound with a starting high concentration of 30 μ M (in the assay final). Column A11 to H11 is used
20 for total binding (Bo) (vehicle-5 μ l of the appropriate DMSO concentration) and column A12 to D12 is used for determination of nonspecific binding. No further preparation is required

Materials:

25 1 M HEPES, pH 7.4, Gibco, Cat. No. 15360-080
Bacitracin, Sigma Catalog. Number. B-0125
Bovine Serum Albumin, Sigma, Cat. No. A-7888
MgCl₂, J.T. Baker 2444-01
CaCl₂, Sigma, Cat. No. C5080
30 MIP1 α , Peprotech, Cat. No. 300-08
Sigmacote, Sigma, Cat. No. SL2
Scintillation Proximity Beads, Wheat Germ Agglutinin, Amersham, Cat No. RPNQ
0001
[¹²⁵I]MIP1 α , NEN (#NEX298)
35 Packard 96 well flat-bottom Optiplate, Cat. No. 6005190

Falcon 96 well round-bottom plate, Cat. No. 3077

TOPSEAL-S, Packard, Cat. No. 6005161

Dimethyl Sulfoxide, EM Science, Cat. No. MX1458-6

Siliconized Pipette tips, Accutip, volume 200-1300uL, Cat. No. P5048-85

5 Siliconized Pipette tips, Bio Plas, Inc., volume 1-200uL, Cat. No. 60828-908

Reagent Reservoir, Elkay, Cat. No. 175-RBAS-000

Assay Buffer Preparation:

50 mM HEPES buffer pH 7.4, 1mM CaCl₂, 5mM MgCl₂(this can be made ahead as a

10 100X stock, 1% BSA, 0.5 mg/ml Bacitracin, Protease inhibitor Cocktail (see preparation above) 100 uL/100 ml, DMSO is added to equal a final concentration of 2% per well (includes compound %DMSO) if needed.

Experimental Details:

15 [¹²⁵I]MIP1 α preparation:

Prepared radioligand dilutions in container treated with Sigmacote

Reconstitute each 50 μ Ci vial with 0.5 ml of deionized water and store at 4°C.

Specific Activity = 2,000 Ci/mmol

Add ~60,000 cpm (0.17 nM) to each assay well in 50uL

20

Bo:

Make a 20% DMSO solution and add 5uls of this to each well in col A11-H11. This gives a final 2% DMSO concentration for the well when added to the 1% in the assay buffer.

25

NSB:

Make a stock dilution of MIP1 α at 100uM using deionized water; aliquot and freeze.

Dilute the MIP-1 α stock solution to a concentration of 2 μ M in the same 20% DMSO solution used above and add 5 μ l to the wells in column A12 to D12 to give a final

30 assay concentration of 100nM. Prepare this in a Sigmacote-treated container

Membrane and SPA Bead preparation-

The final assay concentration for the membrane is 15 μ g per well. SPA beads are prepared by adding 5 ml of assay buffer to a 500 mg vial. The final concentration of

35 SPA beads in the assay is 0.25 mg/well. Membranes and beads are premixed as a

1:1 (membrane:bead) mixture and maintained at mixture at 4°C with constant stirring. 50 μ l of the mixture is added to each assay well. After all reagents have been added to the plates (total assay volume 100 μ l), shake plates for 4 hours at room temperature. After 4 hours, place the plates on the TopCount in a count the plates on the TopCount for 30 sec per well using an appropriate program (i.e., one with a quench curve established for the conditions of the assay).

Data Reduction:

Data reduction is performed using the Microsoft Excel Addins Robofit or Robosage.

For single concentration assays (One Shots), the result of each test well is expressed as % inhibition using the following formula: $100 * (1 - (U1 - C2) / (C1 - C2))$. Where U1 is the unknown sample in cpm observed in a particular well, C1 is the average of column 12 cpm observed in the absence of any added inhibitor, and C2 is the average of column 11 cpm observed in the presence of 1 μ M of MIP1 α .

For concentration-response assays, the result of each test well is expressed as %B/Bo (% total specific binding) using the following formula: $100 * (U1 - C2) / C1 - C2$. Curves were generated by plotting the %B/Bo versus the concentration and the IC₅₀ is derived using the equation $y = V_{max} * (1 - (x^n / (k^n + x^n)))$.

Controls and Standards:

Each plate contains 12 wells of total binding (column A11-H11). The cpm/well are averaged and are used in data reduction as value C1. Each plate also contains 4 wells of non-specific binding (wells A12-D12). The counts of these wells are averaged and used in data reduction as value C2.

A standards plate is included in each experiment. This plate contains a 14-point concentration-response curve (in triplicate) for the standard compound MIP1 α at a starting concentration of 1 μ M. The average historical pK_i obtained with MIP1 α is 7.6.

The relevant biological response field for a single concentration (One Shots) is % inhibition. Inhibition values of >40 or >50% were considered positive responses.

HOS Assay (Also referred to as HOS-LTR-Luciferase Assay)**Materials**

DMEM (GibcoBRL # 10564-011)

5 Trpsin-EDTA (GibcoBRL #25300-054)

Heat inactivated Fetal Bovine Serum (FBS) (Hyclone # SH30070.03)

96-well, black-walled, clear-bottom, tissue culture-treated plates (Costar # 3904)

96-well, clear-walled, clear-bottom tissue culture-treated plates (Costar # 3598)

Phosphate Buffered Saline (PBS) (GibcoBRL #14190-144)

10 Dimethyl Sulfoxide (DMSO) (Sigma # D2650)

Luclite Luciferase Reporter assay (Packard #6016911)

HOS-CD4.CCR5-LTR-Luciferase (Bioresource Registration # 21164): Human

Osteosarcoma cell line engineered to overexpress human CD4 and human CCR5

(AIDS Repository cat# 3318) stably transfected with HIV-1-LTR-Luciferase reporter.

15

Advanced Preparation

Growth and Maintenance of the HOS-CD4.CCR5-LTR-Luciferase cell line:

The cells were propagated in DMEM containing 2% FBS. Cells were split by standard trypsinization when confluency reached 80% (roughly every 2 to 3 days).

20

Titering of virus stocks:

HIV-1 virus stocks were titered in the assay system in order to obtain an estimate of the number of infectious particles per unit volume (described as RLU/ml). Virus stocks were diluted into DMEM containing 2% FBS and assayed as described in the "procedure" section below.

ProcedureBlack-walled 96-well tissue culture plates were seeded with HOS-CD4.CCR5-LTR-Luciferase @ 0.6 to 1.2 x 10³ cells per well in 50ul DMEM containing 2% FBS and30 placed in a humidified incubator @ 37°C, 5% CO₂ overnight. The following day, test compounds were titrated 4-fold at 2X the final concentration in DMEM + 2% FBS + 0.2% DMSO. 50ul of titrated compound was transferred to the HOS cells and the plates were placed in a humidified incubator at 37°C, 5% CO₂ for 1hr. An additional 60ul of 2X titrated compound was transferred to a clear-walled 96-well tissue culture 35 plate and 60ul of HIV (diluted to appropriate m.o.i.) was added to each well and thoroughly mixed. 100ul of the HIV/compound mixture was transferred to the black-

walled plates containing 100ul of cells/compound. The plates were placed in a humidified incubator at 37°C, 5% CO₂ for 72hr. Following the 72 hour incubation, 150ul of supernatant was removed and 50ul of reconstituted LUCLITE (kit reagent) was added to each well. Each plate was sealed and read in a Topcount (Packard) 5 luminometer at 1s/well.

Data Reduction

Relative Light Units (RLU) were expressed as % control

$$(RLU \text{ at drug } [] / RLU \text{ no drug}) * 100 = \% \text{ Control}$$

10 IC₅₀ values were determined by any one of the following four nonlinear regression models:

$$y = V_{max} * (1 - (x^n / (K^n + x^n))) + Y_2$$

$$y = V_{max} * (1 - (x^n / (K^n + x^n)))$$

$$y = V_{max} * (1 - (x / (K + x))) + Y_2$$

15 $y = V_{max} * (1 - (x / (K + x)))$

Where: K is IC₅₀, Y2 is baseline, and N is Hill Coefficient

Each of the compounds of the present invention provides a pIC₅₀ value of at least 5 when tested in each of the above-described assays.

20

Test compounds are employed in free or salt form.

All research complied with the principles of laboratory animal care (NIH publication No. 85-23, revised 1985) and pharmaceutical industry policy on animal use.

25

Although specific embodiments of the present invention have been illustrated and described in detail, the invention is not limited thereto. The above detailed description of preferred embodiments is provided for example only and should not be construed as constituting any limitation of the invention. Modifications will be obvious to those skilled in the art, and all modifications that do not depart from the spirit of the invention are intended to be included within the scope of the appended claims.